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# UNITED STATES SECURITIES AND EXCHANGE COMMISSION

**Washington, DC 20549**

# Form 10-K

(Mark One)

☑ **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 Cambridge, MA** | **02139** |
| *(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 ☑ 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 ☑

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 ☑ 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 ☑ 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 ☑ | 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 ☑

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," "should," "continue" and similar 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.

## 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."*

- *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.

*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

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.

**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>(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<br><br>Celgene: ex-U.S. rights, cross- royalties |
| **Rare genetic disorders of metabolism:** | | | | |
| AG-348<br>(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 (α-ketoglutarate), both of which are critically important for cellular function and the creation of energy. In humans, there are three forms of the IDH enzyme, IDH1, IDH2, and IDH3, but only IDH1 and IDH2 appear to be mutated in cancers. IDH1 and IDH2 catalyze the

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

Using our proprietary metabolic platform, we and our collaborators examined the mutated pathway and discovered that the mutated IDH enzymes had adopted a novel "gain of function" activity that allows only the mutated IDH enzyme to produce large amounts of a metabolite called 2-hydroxygluturate, or 2HG. We believe that the excessive levels of the metabolite 2HG produced by the tumor fuel cancer growth and survival via multiple cellular changes that lead to a block in cell maturation, or differentiation. We believe that inhibition of these mutated proteins will lead to clinical benefit for the subset of cancer patients whose tumors carry these mutations. We have identified selective development candidates that target and inhibit the mutated forms of IDH1 and IDH2. To date, our 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

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

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

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.

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.

*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.

- *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

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,

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.

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.

*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.

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.

*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

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.

*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.

*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.

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

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.

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.

*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

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

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;

- 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

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

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

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

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.

***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;

- not obtain marketing approval at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings, including boxed warnings;
- be subject to additional post-marketing testing requirements; or
- have the medicine removed from the market after obtaining marketing approval.

Product development costs will also increase if we or our collaborators experience delays in testing or marketing approvals. We do not know whether any clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates, could allow our competitors to bring products to market before we do, and could impair our ability to successfully commercialize our product candidates, any of which may harm our business and results of operations.

***If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.***

We or our collaborators may not be able to initiate or continue clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or analogous regulatory authorities outside the United States. Enrollment may be particularly challenging for some of the orphan diseases we target in our RGD programs. In addition, some of our competitors may have ongoing clinical trials for product candidates that would treat the same indications as our product candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates.

Patient enrollment is also affected by other factors including:

- severity of the disease under investigation;
- availability and efficacy of approved medications for the disease under investigation;
- eligibility criteria for the study in question;
- perceived risks and benefits of the product candidate under study;
- efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment; and
- proximity and availability of clinical trial sites for prospective patients.

Furthermore, we rely on CROs and clinical trial sites to ensure the proper and timely conduct of our clinical trials and while we have agreements governing their committed activities, we have limited influence over their actual performance. Our or our collaborators' inability to enroll a sufficient number of patients for our clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, which would cause the value of our company to decline and limit our ability to obtain additional financing.

***If serious adverse side effects or unexpected characteristics are identified during the development of our product candidates, we may need to abandon or limit our development of some of our product candidates.***

All of our product candidates are still in early-clinical stage development and their risk of failure is high. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will

receive marketing approval. If our product candidates are associated with undesirable side effects or have characteristics that are unexpected, we may need to abandon their development or limit development to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Many compounds that initially showed promise in early stage testing for treating cancer, RGDs or other diseases have later been found to cause side effects that prevented further development of the compound.

***We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.***

Because we have limited financial and managerial resources, we focus on research programs and product candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial medicines or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable medicines. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

Under our collaboration agreement with Celgene, we have the right, exercisable during a specified period following FDA acceptance of the applicable investigational new drug application, or IND, to convert one of every three co-commercialized licensed programs into a split licensed program, for which we retain the United States rights. Due to the limited exercise period, we may have to choose whether a co-commercialized program will be a split licensed program before we have as much information as we would like on another co-commercialized program, including whether and when such co-commercialized program may receive FDA acceptance of the applicable IND. Our IDH2 program is not a split licensed program. We have chosen AG-120, and our IDH1 program, as our first split licensed program. As a result of such incomplete information or due to incorrect analysis by us, we may select a split licensed program that later proves to have less commercial potential than an alternative or none at all.

***If we are unable to successfully develop companion diagnostics for our therapeutic product candidates, or experience significant delays in doing so, we may not realize the full commercial potential of our therapeutics.***

Because we are focused on precision medicine, in which predictive biomarkers will be used to identify the right patients for our drug candidates, we believe that our success may depend, in part, on our ability to develop companion diagnostics, which are assays or tests to identify an appropriate patient population for these drug candidates. There has been limited success to date industry-wide in developing these types of companion diagnostics. To be successful, we need to address a number of scientific, technical and logistical challenges. We have little experience in the development of diagnostics and may not be successful in developing appropriate diagnostics to pair with any of our therapeutic product candidates that receive marketing approval. Companion diagnostics are subject to regulation by the FDA and similar regulatory authorities outside the United States as medical devices and require separate regulatory approval prior to commercialization. Given our limited experience in developing diagnostics, we expect to rely in part or in whole on third parties for their design and manufacture. We also depend on Celgene for the development of diagnostics for some of our cancer therapeutic product candidates. If we, Celgene or any third parties that we or Celgene engage to assist us, are unable to successfully develop companion diagnostics for our therapeutic product candidates, or experience delays in doing so:

- the development of our therapeutic product candidates may be adversely affected if we are unable to appropriately select patients for enrollment in our clinical trials;
- our therapeutic product candidates may not receive marketing approval if safe and effective use of a therapeutic product candidate depends on an *in vitro* diagnostic; and

- we may not realize the full commercial potential of any therapeutics that receive marketing approval if, among other reasons, we are unable to appropriately select patients who are likely to benefit from therapy with our medicines.

As a result, our business would be harmed, possibly materially.

***Even if any of our product candidates receive marketing approval, they may fail to achieve the degree of market acceptance by physicians, patients, healthcare payors and others in the medical community necessary for commercial success.***

If any of our product candidates receive marketing approval, they may nonetheless fail to gain sufficient market acceptance by physicians, patients, healthcare payors and others in the medical community. For example, current cancer treatments like chemotherapy and radiation therapy are well established in the medical community, and doctors may continue to rely on these treatments. If our product candidates do not achieve an adequate level of acceptance, we may not generate significant product revenues and we may not become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- efficacy and potential advantages compared to alternative treatments;
- the approval, availability, market acceptance and reimbursement for the companion diagnostic;
- the ability to offer our medicines for sale at competitive prices;
- convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support;
- sufficient third-party coverage or reimbursement; and
- the prevalence and severity of any side effects.

***If, in the future, we are unable to establish sales and marketing capabilities or enter into agreements with third parties to sell and market our product candidates, we may not be successful in commercializing our product candidates if and when they are approved.***

We do not have a sales or marketing infrastructure and have no experience in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for any approved medicine for which we retain sales and marketing responsibilities, we must either develop a sales and marketing organization or outsource these functions to other third parties. In the future, we may choose to build a focused sales and marketing infrastructure to sell, or participate in sales activities with our collaborators for, some of our product candidates if and when they are approved.

There are risks involved with both establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize our medicines on our own include:

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future medicines;

- the lack of complementary medicines to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we enter into arrangements with third parties to perform sales, marketing and distribution services, our product revenues or the profitability of these product revenues to us are likely to be lower than if we were to market and sell any medicines that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market our product candidates or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our medicines effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

***We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do.***

The development and commercialization of new drug products is highly competitive. We face competition with respect to our current product candidates, and we and our collaborators will face competition with respect to any product candidates that we or they may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of the disease indications for which we are developing our product candidates, such as acute myelogenous leukemia and high risk myelodysplasia. Some of these competitive products and therapies are based on scientific approaches that are the same as or similar to our approach, and others are based on entirely different approaches, for example, in the area of RGDs. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

We are developing our initial product candidates for the treatment of cancer. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy, and cancer drugs are frequently prescribed off-label by healthcare professionals. 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. Insurers and other third-party payors may also encourage the use of generic products. We expect that if our product candidates are approved, they will be priced at a significant premium over competitive generic products. This may make it difficult for us to achieve our business strategy of using our product candidates in combination with existing therapies or replacing existing therapies with our product candidates.

We are also pursuing product candidates to treat patients with RGDs. There are a variety of treatment options available, including a number of marketed enzyme replacement therapies, for treating patients with RGDs. 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.

There are also a number of product candidates in preclinical development by third parties to treat cancer and RGDs by targeting cellular metabolism. These companies include large pharmaceutical companies, including AstraZeneca plc, Eli Lilly and Company, Roche Holdings Inc. and its subsidiary Genentech, Inc., GlaxoSmithKline plc, Merck & Co., Novartis International AG, Pfizer, Inc., and Genzyme, a Sanofi company.

There are also biotechnology companies of various size that are developing therapies to target cellular metabolism, including Alexion Pharmaceuticals, Inc., BioMarin Pharmaceutical Inc., Calithera Biosciences, Inc., Cornerstone Pharmaceuticals, Inc., Forma Therapeutics Holdings LLC, Shire Biochem Inc. and Raze Therapeutics. Our competitors may develop products that are more effective, safer, more convenient or less costly than any that we are developing or that would render our product candidates obsolete or non-competitive. In addition, our competitors may discover biomarkers that more efficiently measure metabolic pathways than our methods, which may give them a competitive advantage in developing potential products. Our competitors may also obtain marketing approval from the FDA or other regulatory authorities for their products 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.

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

***Even if we or our collaborators are able to commercialize any product candidates, such products may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, which would harm our business.***

The regulations that govern marketing approvals, pricing and reimbursement for new medicines vary widely from country to country. In the United States, recently enacted legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a medicine before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we or our collaborators might obtain marketing approval for a medicine in a particular country, but then be subject to price regulations that delay our commercial launch of the medicine, possibly for lengthy time periods, and negatively impact the revenues we or our collaborators are able to generate from the sale of the medicine in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if our product candidates obtain marketing approval.

Our and our collaborators' ability to commercialize any medicines successfully also will depend in part on the extent to which reimbursement for these medicines and related treatments will be available from government health administration authorities, private health insurers and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. We cannot be sure that reimbursement will be available for any medicine that we or our collaborators commercialize and, if reimbursement is available, the level of reimbursement. Reimbursement may impact the demand for, or the price of, any product candidate for which we obtain marketing approval. If reimbursement is not available or is available only to limited levels, we or our collaborators may not be able to successfully commercialize any product candidate for which we or they obtain marketing approval.

There may be significant delays in obtaining reimbursement for newly approved medicines, and coverage may be more limited than the purposes for which the medicine is approved by the FDA or similar regulatory authorities outside the United States. Moreover, eligibility for reimbursement does not imply that any medicine will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Interim reimbursement levels for new medicines, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the medicine and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost medicines and may be incorporated into existing payments for other services. Net prices for medicines may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of medicines from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our or our collaborators' inability to promptly obtain coverage and profitable payment rates from both government-funded and private payors for any approved medicines that we or they develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize medicines and our overall financial condition.

***Product liability lawsuits against us or our collaborators could cause us or our collaborators to incur substantial liabilities and could limit commercialization of any medicines that we or they may develop.***

We and our collaborators face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials and will face an even greater risk if we or they commercially sell any medicines that we or they may develop. If we or our collaborators cannot successfully defend ourselves or themselves against claims that our product candidates or medicines caused injuries, we could incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidates or medicines that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend the related litigation;
- substantial monetary awards to trial participants or patients;
- loss of revenue; and
- the inability to commercialize any medicines that we may develop.

Although we maintain product liability insurance coverage, it may not be adequate to cover all liabilities that we may incur. We anticipate that we will need to increase our insurance coverage when we continue clinical trials and if we successfully commercialize any medicine. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. In addition, if one of our collaboration partners were to become subject to product liability claims or were unable to successfully defend themselves against such claims, any such collaboration partner could be more likely to terminate such relationship with us and therefore substantially limit the commercial potential of our products.

***If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.***

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological and radioactive materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury

from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

***We rely significantly on information technology and any failure, inadequacy, interruption or security lapse of that technology, including any cyber security incidents, could harm our ability to operate our business effectively.***

Despite the implementation of security measures, our internal computer systems and those of third parties with which we contract are vulnerable to damage from cyber-attacks, computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. System failures, accidents or security breaches could cause interruptions in our operations, and could result in a material disruption of our clinical and commercialization activities and business operations, in addition to possibly requiring substantial expenditures of resources to remedy. The loss of clinical trial data could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and our product research, development and commercialization efforts could be delayed.

**Risks Related to Our Dependence on Third Parties**

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

In April 2010, we entered into our collaboration with Celgene focused on cancer metabolism. The collaboration involves a complex allocation of rights, provides for milestone payments to us based on the achievement of specified clinical development, regulatory and commercial milestones, provides for additional payments upon Celgene's election to extend the term of the discovery phase, provides us with royalty-based revenue if certain product candidates are successfully commercialized and provides for cost reimbursements of certain development activities. We cannot predict the success of the collaboration.

We may seek other third-party collaborators for the development and commercialization of our product candidates. Our likely collaborators for any collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. If we enter into any such arrangements with any third parties, we will likely have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements.

Collaborations involving our product candidates, including our collaboration with Celgene, pose the following risks to us:

- Collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations. For example, under our collaboration with Celgene, development and

commercialization plans and strategies for licensed programs, such as AG-221, will be conducted in accordance with a plan and budget approved by a joint committee comprised of equal numbers of representatives from each of us and Celgene, which Celgene has final decision-making authority.

- Collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborator's strategic focus or available funding or external factors such as an acquisition that diverts resources or creates competing priorities. For example, it is possible for Celgene to elect not to progress into preclinical development a product candidate that we have nominated and the joint research committee, or JRC, confirmed, without triggering a termination of the collaboration arrangement.
- Collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing. For example, under our agreement with Celgene, it is possible for Celgene to terminate the agreement, upon 90 days prior written notice, with respect to any product candidate at any point in the research, development and clinical trial process, without triggering a termination of the remainder of the collaboration arrangement.
- Collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our medicines or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours.
- A collaborator with marketing and distribution rights to one or more medicines may not commit sufficient resources to the marketing and distribution of such medicine or medicines.
- Collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our proprietary information or expose us to potential litigation. For example, Celgene has the first right to maintain or defend our intellectual property rights under our collaboration arrangement with respect to certain licensed programs and, although we may have the right to assume the maintenance and defense of our intellectual property rights if Celgene does not, our ability to do so may be compromised by Celgene's actions.
- Disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of our medicines or product candidates or that result in costly litigation or arbitration that diverts management attention and resources.
- We may lose certain valuable rights under circumstances identified in our collaborations, including, in the case of our agreement with Celgene, if we undergo a change of control.
- Collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates. For example, Celgene can terminate its agreement with us, in its entirety or with respect to any program, upon 90 days' notice and can terminate the entire agreement with us in connection with a material breach of the agreement by us that remains uncured for 60 days.
- Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If a present or future collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program under such collaboration could be delayed, diminished or terminated.

***We may seek to establish additional collaborations, and, if we are not able to establish them on commercially reasonable terms, we may have to alter our development and commercialization plans.***

Our drug development programs and the potential commercialization of our product candidates will require substantial additional cash to fund expenses. For some of our product candidates, we may decide to collaborate

with additional pharmaceutical and biotechnology companies for the development and potential commercialization of those product candidates.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such collaboration could be more attractive than the one with us for our product candidate.

We may also be restricted under existing collaboration agreements from entering into future agreements on certain terms with potential collaborators. For example, during the discovery phase of our collaboration with Celgene, we may not directly or indirectly develop, manufacture or commercialize, except pursuant to the agreement, any medicine or product candidate for any cancer indication: with specified activity against certain metabolic targets except in connection with certain 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. 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 medicine or product candidate 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.

Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of the product candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

***We rely and expect to continue to rely on third parties to conduct our clinical trials and some aspects of our research and preclinical testing, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials, research or testing.***

We expect to rely on third parties, such as contract research organizations, or CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials. We currently rely and expect to continue to rely on third parties to conduct some aspects of our research and preclinical testing. Any of these third parties may terminate their engagements with us, some in the event of an uncured material breach and some at any time. If any of our relationships with these third parties terminate, we may not be able to enter into arrangements with alternative third-parties or to do so on commercially reasonable terms. Switching or adding additional third parties involves additional cost and requires management time and focus. In addition, there is a

natural transition period when a new third party commences work. As a result, delays may occur in our product development activities. Although we seek to carefully manage our relationships with our CROs, we could encounter similar challenges or delays in the future and these challenges or delays could have a material adverse impact on our business, financial condition and prospects.

Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on third parties does not relieve us of our regulatory responsibilities. We and these third parties are required to comply with current good clinical practices, or cGCP, which are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area, or EEA, and comparable foreign regulatory authorities for all of our products in clinical development. Regulatory authorities enforce these cGCPs through periodic inspections of trial sponsors, principal investigators and trial sites. If we or any of these third parties fail to comply with applicable cGCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, the European Medicines Agency, or EMA, or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials comply with cGCP regulations. In addition, our clinical trials must be conducted with product produced under current good manufacturing practices, or cGMP, regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, clinicaltrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. In addition, these third parties are not our employees, and except for remedies available to us under our agreements with such third parties, we cannot control whether or not they devote sufficient time and resources to our on-going clinical, nonclinical and preclinical programs. If these third parties do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our medicines. As a result, our results of operations and the commercial prospects for our medicines would be harmed, our costs could increase and our ability to generate revenues could be delayed.

We also expect to rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our product candidates or commercialization of our medicines, producing additional losses and depriving us of potential product revenue.

***We contract with third parties for the manufacture of our product candidates for preclinical and early clinical testing and expect to continue to do so for late-stage clinical trials and for commercialization. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or medicines or that such supply will not be available to us at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.***

We do not have any manufacturing facilities. We currently rely, and expect to continue to rely, on third-party manufacturers for the manufacture of our product candidates for preclinical and clinical testing and for commercial supply of any of these product candidates for which we or our collaborators obtain marketing approval. To date, we have obtained materials for AG-221, AG-120 and AG-348 for our ongoing and planned phase 1 testing from third party manufacturers. We do not have any long term supply agreements with the third-party manufacturers, and we purchase our required drug supply on a purchase order basis.

We may be unable to establish any agreements with third-party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- reliance on the third party for regulatory compliance and quality assurance;
- the possible breach of the manufacturing agreement by the third party;
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us; and
- reliance on the third party for regulatory compliance, quality assurance, and safety and pharmacovigilance reporting.

Third-party manufacturers may not be able to comply with current good manufacturing practices, or cGMP, regulations or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or medicines, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our medicines and harm our business and results of operations.

Any medicines that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply for bulk drug substances. If any one of our current contract manufacturer cannot perform as agreed, we may be required to replace that manufacturer. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur added costs and delays in identifying and qualifying any such replacement.

Our current and anticipated future dependence upon others for the manufacture of our product candidates or medicines may adversely affect our future profit margins and our ability to commercialize any medicines that receive marketing approval on a timely and competitive basis.

**Risks Related to Our Intellectual Property**

***If we are unable to obtain and maintain patent or trade secret protection for our medicines and technology, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize medicines and technology similar or identical to ours, and our ability to successfully commercialize our medicines and technology may be adversely affected.***

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary medicines and technology. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies and medicines that are important to our business. We currently have patent protection for one of our lead product candidates in the United States, and do not own or license any issued patents for our other lead product candidates in major markets such as the United States and Europe.

The patent prosecution process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Although we enter into non-disclosure and confidentiality agreements with parties who have access to

patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, contract research organizations, contract manufacturers, consultants, advisors and other third parties, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection.

We may in the future license patent rights that are valuable to our business from third parties, in which event we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology or medicines underlying such licenses. We cannot be certain that these patents and applications will be prosecuted and enforced in a manner consistent with the best interests of our business. If any such licensors fail to maintain such patents, or lose rights to those patents, the rights we have licensed may be reduced or eliminated and our right to develop and commercialize any of our products that are the subject of such licensed rights could be adversely affected. In addition to the foregoing, the risks associated with patent rights that we license from third parties also apply to patent rights we own.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which protect our technology or medicines or which effectively prevent others from commercializing competitive technologies and medicines. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection.

The laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore we cannot be certain that we were the first to make the inventions claimed in our owned or any licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions.

Assuming the other requirements for patentability are met, prior to March 2013, in the United States, the first to make the claimed invention was entitled to the patent, while outside the United States, the first to file a patent application was entitled to the patent. Beginning in March 2013, the United States transitioned to a first inventor to file system in which, assuming the other requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent. We may be subject to a third party preissuance submission of prior art to the U.S. Patent and Trademark Office, or become involved in opposition, derivation, revocation, reexamination, post-grant and *inter partes* review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize medicines without infringing third-party patent rights.

Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us or otherwise provide us with any competitive advantage. Our competitors or other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and medicines. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might

expire before or shortly after such candidates are commercialized. As a result, our intellectual property may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

***We may become involved in lawsuits to protect or enforce our patents and other intellectual property rights, which could be expensive, time consuming and unsuccessful.***

Competitors may infringe our patents and other intellectual property rights. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

***Third parties may initiate legal proceedings alleging that we or our collaborators are infringing their intellectual property rights, the outcome of which would be uncertain and could have a material adverse effect on the success of our business.***

Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights and intellectual property of third parties. The biotechnology and pharmaceutical industries are characterized by extensive litigation regarding patents and other intellectual property rights. We have in the past and may in the future become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our medicines and technology, including interference proceedings before the U.S. Patent and Trademark Office. For example, in 2011, The Leonard and Madlyn Abramson Family Cancer Research Institute at the Abramson Cancer Center of the University of Pennsylvania initiated a lawsuit against us, one of our founders, Craig B. Thompson, M.D., and Celgene, alleging misappropriation of intellectual property and, in 2012, the Trustees of the University of Pennsylvania initiated a similar lawsuit against us and Dr. Thompson. Each of these lawsuits was settled in 2012. No other legal proceedings have been filed against us to date. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. If we or one of our collaborators are found to infringe a third party's intellectual property rights, we or they could be required to obtain a license from such third party to continue developing and marketing our medicines and technology. However, we or our collaborator may not be able to obtain any required license on commercially reasonable terms or at all. Even if we or our collaborator were able to obtain a license, it could be non-exclusive, thereby giving our competitors and other third parties access to the same technologies licensed to us. We or our collaborators could be forced, including by court order, to cease developing and commercializing the infringing technology or medicine. In addition, we or our collaborators could be found liable for monetary damages. A finding of infringement could prevent us or our collaborators from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we or our collaborators have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

***We may be subject to claims that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.***

Many of our employees, consultants or advisors are currently or were previously employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these individuals have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or

personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management. Other than the litigation initiated by the Leonard and Madlyn Abramson Family Cancer Research Institute at the Abramson Cancer Center of the University of Pennsylvania and by the Trustees of the University of Pennsylvania described above, no such claims have been filed against us to date.

***Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities.***

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

***If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.***

In addition to seeking patents for some of our technology and medicines, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. 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.

We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract research organizations, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third party, our competitive position would be harmed.

**Risks Related to Regulatory Approval of Our Product Candidates and Other Legal Compliance Matters**

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

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory

agencies in the United States and by comparable authorities in other countries. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. We and our collaborators have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction. We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party contract research organizations to assist us in this process. Securing regulatory approval requires the submission of extensive preclinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing regulatory approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive, may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. The FDA and comparable authorities in other countries have substantial discretion in the approval process and may refuse to accept any application or may decide that our data is insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we or our collaborators ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved medicine not commercially viable.

If we or our collaborators experience delays in obtaining approval or if we or they fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenues will be materially impaired.

***A Fast Track designation by the FDA may not actually lead to a faster development or regulatory review or approval process.***

In the United States, AG-221 received Fast Track designation for treatment of patients with AML that harbor an IDH2 mutation. If a drug is intended for the treatment of a serious or life-threatening disease or condition and the drug demonstrates the potential to address unmet medical needs for this disease or condition, the drug sponsor may apply for FDA Fast Track designation. The FDA has broad discretion whether or not to grant Fast Track designation, so even if we believe a particular product candidate is eligible for such designation, the FDA could decide not to grant it. Even though AG-221 has received fast track designation for treatment of patients with AML that harbor an IDH2 mutation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw Fast Track designation if it believes that the designation is no longer supported by data from our clinical development program.

***Failure to obtain marketing approval in international jurisdictions would prevent our medicines from being marketed in such jurisdictions.***

In order to market and sell our medicines in the European Union and many other jurisdictions, we or our collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We or our collaborators may not

obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our medicines in any market.

***Any product candidate for which we or our collaborators obtain marketing approval could be subject to restrictions or withdrawal from the market and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our medicines, when and if any of them are approved.***

Any product candidate for which we or our collaborators obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such medicine, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to quality control, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and recordkeeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the medicine may be marketed or to the conditions of approval, or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the medicine. The FDA closely regulates the post-approval marketing and promotion of medicines to ensure that they are marketed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding off-label use and if we do not market our medicines for their approved indications, we may be subject to enforcement action for off-label marketing.

In addition, later discovery of previously unknown problems with our medicines, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including:

- restrictions on such medicines, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a medicine;
- restrictions on distribution or use of a medicine;
- requirements to conduct post-marketing clinical trials;
- warning or untitled letters;
- withdrawal of the medicines from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of medicines;
- fines, restitution or disgorgement of profits or revenue;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of our medicines;
- product seizure; and
- injunctions or the imposition of civil or criminal penalties.

***Our relationships with customers and third-party payors will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.***

Healthcare providers, physicians and third-party payors play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute our medicines for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations, include the following:

- the federal healthcare anti-kickback statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under federal and state healthcare programs such as Medicare and Medicaid;
- the federal False Claims Act imposes criminal and civil penalties, including civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, as amended by the Health Information Technology for Economic and Clinical Health Act, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;
- the federal transparency requirements under the Affordable Care Act requires manufacturers of drugs, devices, biologics and medical supplies to report to the Department of Health and Human Services information related to physician payments and other transfers of value and physician ownership and investment interests; and
- analogous state laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, and some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures.

Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other providers or entities with whom we expect to do business are found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

***Recently enacted and future legislation may increase the difficulty and cost for us or our collaborators to obtain marketing approval of and commercialize our product candidates and affect the prices we or they may obtain.***

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our or our collaborators ability to profitably sell any product candidates for which we or they obtain marketing approval.

In the United States, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or Medicare Modernization Act, changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and introduced a new reimbursement methodology based on average sales prices for physician administered drugs. In addition, this legislation provided authority for limiting the number of drugs that will be covered in any therapeutic class. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and price that we receive for any approved products. While the Medicare Modernization Act applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the Medicare Modernization Act may result in a similar reduction in payments from private payors.

More recently, in March 2010, U.S. President Barack Obama signed into law the Affordable Care Act, a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for health care and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. Effective October 1, 2010, the Affordable Care Act revises the definition of "average manufacturer price" for reporting purposes, which could increase the amount of Medicaid drug rebates to states. Further, the new law imposes a significant annual fee on companies that manufacture or import branded prescription drug products. Substantial new provisions affecting compliance have also been enacted, which may affect our business practices with health care practitioners. We will not know the full effects of the Affordable Care Act until applicable federal and state agencies issue regulations or guidance under the new law. Although it is too early to determine the effect of the Affordable Care Act, the new law appears likely to continue the pressure on pharmaceutical pricing, especially under the Medicare program, and may also increase our regulatory burdens and operating costs. Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

**Risks Related to Employee Matters and Managing Growth**

***Our future success depends on our ability to retain our chief executive officer and other key executives and to attract, retain and motivate qualified personnel.***

We are highly dependent on David Schenkein, M.D., our chief executive officer, J. Duncan Higgons, our chief operating officer, Scott Biller, Ph.D., our chief scientific officer, and Christopher Bowden, M.D., our chief medical officer, as well as the other principal members of our management and scientific teams. Drs. Schenkein, Biller and Bowden, and Mr. Higgons are employed "at will," meaning we or they may terminate the employment relationship at any time. We do not maintain "key person" insurance for any of our executives or other employees. The loss of the services of any of these persons could impede the achievement of our research, development and commercialization objectives.

Recruiting and retaining qualified scientific, clinical, manufacturing and sales and marketing personnel will also be critical to our success. We may not be able to attract and retain these personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors, including our scientific co-founders, may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us.

***Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could have a material adverse effect on our business.***

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA regulations, provide accurate information to the FDA, comply with manufacturing standards we have established, comply with federal and state health-care fraud and abuse laws and regulations, report financial information or data accurately, disclose unauthorized activities to us, or comply with securities laws. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, including for illegal insider trading activities, which could result in regulatory sanctions and serious harm to our reputation. We have adopted a Code of Business Ethics, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant fines or other sanctions.

***We expect to expand our development, regulatory and future sales and marketing capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.***

We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of drug development, regulatory affairs and sales and marketing. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expected expansion of our operations or recruit and train additional qualified personnel. Moreover, the expected physical expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

**Risks Related to Our Common Stock**

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

As of January 31, 2015 our executive officers, directors and a small number of our stockholders own more than a majority of our outstanding common stock. As a result, if these stockholders were to choose to act together, they would be able to control all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would control the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of voting power could delay or prevent an acquisition of our company on terms that other stockholders may desire.

***Provisions in our corporate charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.***

Provisions in our corporate charter and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- establish a classified board of directors such that not all members of the board are elected at one time;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from the board;
- establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;
- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call stockholder meetings;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a shareholder rights plan, or so-called "poison pill," that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner.

***If securities analysts do not publish research or reports about our business or if they publish negative, or inaccurate, evaluations of our stock, the price of our stock and trading volume could decline.***

The trading market for our common stock relies in part on the research and reports that industry or financial analysts publish about us or our business. If one or more of the analysts covering our business downgrade their evaluations of our stock, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price and trading volume to decline.

***An active trading market for our common stock may not be sustained.***

Although our common stock is listed on the NASDAQ Global Select Market, an active trading market for our shares may not be sustained. If an active market for our common stock does not continue, it may be difficult for our stockholders to sell their shares without depressing the market price for the shares or sell their shares at all. Any inactive trading market for our common stock may also impair our ability to raise capital to continue to fund our operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

***The price of our common stock may be volatile and fluctuate substantially, which could result in substantial losses for purchasers of our common stock.***

The trading price of our common stock has been, and may continue to be, volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. Since our initial public offering in July 2013 the price of our common stock on the NASDAQ Global Select Market has ranged from $15.77 per share to $138.85 per share. The stock market in general and the market for biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. The market price for our common stock may be influenced by many factors, including:

- the success of competitive products or technologies;
- results of clinical trials of our product candidates or those of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates or medicines;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this “Risk factors” section.

***Sales of a substantial number of shares of our common stock in the public market could cause our stock price to fall.***

Persons who were our stockholders prior to our initial public offering continue to hold a substantial number of shares of our common stock. If such persons sell, or indicate an intention to sell, substantial amounts of our common stock in the public market, the trading price of our common stock could decline.

In addition, shares of common stock that are either subject to outstanding options or reserved for future issuance under our stock incentive plans will become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules and Rule 144 and Rule 701 under the Securities Act of 1933, as amended, or the Securities Act, and, in any event, we have filed a registration statement permitting shares of common stock issued on exercise of options to be freely sold in the public market. If these additional shares of common stock are sold, or if it is perceived that they will be sold, in the public market, the trading price of our common stock could decline.

Certain holders of our common stock are entitled to rights with respect to the registration of their shares under the Securities Act. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act, except for shares held by affiliates. Any sales of securities by these stockholders could have a material adverse effect on the trading price of our common stock.

***Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our stock incentive plans, could result in additional dilution of the percentage ownership of our stockholders and could cause our stock price to fall.***

We expect that significant additional capital will be needed in the future to continue our planned operations. To raise capital, we may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities in more than one transaction, investors may be materially diluted by subsequent sales. Such sales may also result in material dilution to our existing stockholders, and new investors could gain rights, preferences and privileges senior to those of holders of our common stock.

Pursuant to our stock incentive plan(s), our compensation committee (or its designee) and board of directors are authorized to grant equity-based incentive awards to our employees, directors and consultants. As of February 20, 2015, the number of shares of our common stock available for future grant under our 2013 Stock Incentive Plan, or the 2013 Plan, is 2,019,970.

The number of shares of our common stock reserved for issuance under our 2013 Plan will be increased (i) from time to time by the number of shares of our common stock forfeited upon the expiration, cancellation, forfeiture, cash settlement or other termination of awards under our 2007 Stock Incentive Plan, and (ii) an annual increase, to be added on the first day of each fiscal year, beginning with the fiscal year ending December 31, 2014 and continuing until the expiration of the 2013 Plan, equal to the lesser of (x) 2,000,000 shares of our common stock, (y) 4% of the outstanding shares on such date or (z) an amount determined by our board of directors. Future option grants and issuances of common stock under our 2013 Plan may have an adverse effect on the market price of our common stock.

***Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.***

Under Section 382 of the Internal Revenue Code of 1986, as amended, if a company undergoes an "ownership change," generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes (such as research tax credits) to offset its post-change taxable income or taxes may be limited. Our prior equity offerings and other changes in our stock ownership, some of which are outside of our control, may have resulted or could in the future result in an ownership change. For example, in 2012, we completed a review of our changes in ownership through December 31, 2011, and determined that we had two qualified ownership changes since inception. The changes of ownership will result in net operating loss and research and development credit carryforwards that we expect to expire unutilized. If additional limitations were to apply, utilization of a portion of our net operating loss and tax credit carryforwards could be further limited in future periods and a portion of the carryforwards could expire before being available to reduce future income tax liabilities.

***We incur increased costs as a result of operating as a public company, and our management is now required to devote substantial time to new compliance initiatives and corporate governance practices.***

As a public company, and particularly as of January 1, 2015 when we ceased to be an "emerging growth company," we do and will continue to incur significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of The NASDAQ Global Select Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased our legal and financial compliance costs and will make some activities more time-consuming and costly especially as we are no longer an "emerging growth company", as defined in the Jumpstart Our Business Startups Act of 2012, and are no longer able to take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are "emerging growth companies" and were applicable to us prior to January 1, 2015.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, as of January 1, 2015 we are required to furnish with our periodic Exchange Act reports a report by our management on our internal control over financial reporting. As of January 1, 2015, because we are no longer an emerging growth company, we are required to include with our annual report an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we have been engaged in a process to document and evaluate our internal control over financial reporting, which has been, and will continue to be, both costly and challenging. In this regard, we will need to continue to dedicate internal resources, engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, from time to time, that our internal control over financial reporting is effective as required by Section 404. If we identify one or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

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

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

**Item 1B. Unresolved Staff Comments**

None.

**Item 2. Properties**

On September 15, 2014, we entered into an operating lease agreement, or the Lease, for approximately 74,500 square feet of office and laboratory space located at 88 Sidney Street, Cambridge, Massachusetts. Concurrently, we also entered into an agreement to terminate our existing lease under which we currently lease approximately 38,500 square feet of office and laboratory space located at 38 Sidney Street, Cambridge, Massachusetts. On November 21, 2014, we entered into a first amendment to the Lease, or the Lease Amendment, to expand the rentable square footage of the leased space at 88 Sidney Street to approximately 113,200 square feet. The date on which we will become responsible for paying rent under the Lease, as amended by the Lease Amendment, or the Commencement Date, will be the earlier of May 15, 2015 or the date upon which we first begin conducting business at the new location. Our existing lease at 38 Sidney Street will terminate thirty days after the Commencement Date. The initial lease term will be for a period of seven years from the Commencement Date. At the end of the lease term, we have the option to extend the Lease for two consecutive terms of five years at the fair market rent at the time of the extension.

We believe our existing facilities are adequate for our current needs and that additional space will be available in the future on commercially reasonable terms as needed.

**Item 3. Legal Proceedings**

From time to time, we may be party to various legal claims and legal proceedings or other disputes incidental to our business, such as intellectual property or contract matters. For a discussion of the risks associated with intellectual property legal proceedings and other disputes, see Item 1A. "Risk Factors —*Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities.*

We are not currently a party to any material legal proceedings, and we do not currently have any contingencies related to ongoing legal matters.

**Item 4. Mine Safety Disclosures**

None.

## PART II

### Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

#### Market Information

Our common stock has been publicly traded on the NASDAQ Global Select Market under the symbol "AGIO" since July 24, 2013. Prior to that time, there was no public market for our common stock. The following table sets forth the high and low sales prices of our common stock as reported on the NASDAQ Global Select Market for each quarter in the year ended December 31, 2014 and for the period July 24, 2013 through December 31, 2013.

| 2014 | High | Low |
|---|---|---|
| First Quarter | $ 49.79 | $ 21.70 |
| Second Quarter | $ 50.37 | $ 31.42 |
| Third Quarter | $ 69.50 | $ 33.01 |
| Fourth Quarter | $ 124.39 | $ 58.55 |

| 2013 | High | Low |
|---|---|---|
| Third Quarter (Beginning July 24, 2013) | $ 33.45 | $ 22.34 |
| Fourth Quarter | $ 33.59 | $ 15.77 |

#### Holders

As of February 20, 2015, there were approximately 30 holders of record of our common stock. This number does not include beneficial owners whose shares are held by nominees in street name.

#### Dividends

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

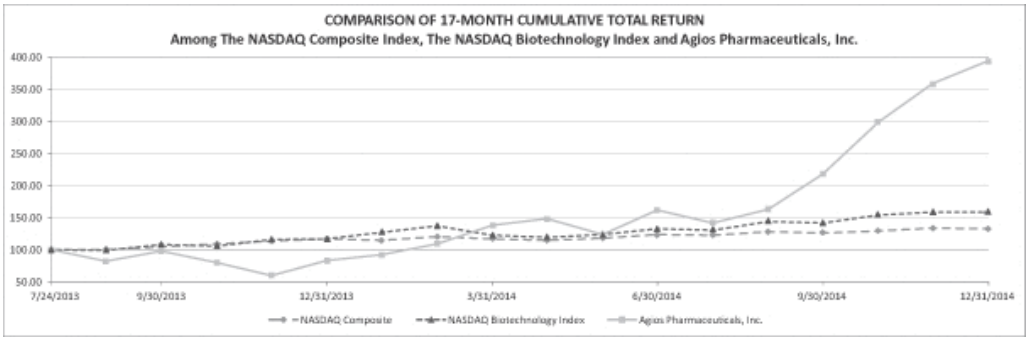
#### Securities Authorized for Issuance under Equity Compensation Plans

Information about our equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report on Form 10-K.

#### Performance Graph

The following performance graph and related information shall not be deemed to be "soliciting material" or to be "filed" with the SEC for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, or otherwise subject to the liabilities under that Section, nor shall such information be incorporated by reference into any future filing under the Exchange Act or the Securities Act of 1933, as amended, or the Securities Act, except to the extent that we specifically incorporate it by reference into such filing.

The following graph compares the performance of our common stock to The NASDAQ Composite Index and to The NASDAQ Biotechnology Index from July 24, 2013 (the first date that shares of our common stock were publicly traded) through December 31, 2014. The comparison assumes $100 was invested after the market closed on July 24, 2013 in our common stock and in each of the foregoing indices, and it assumes reinvestment of dividends, if any. The stock price performance included in this graph is not necessarily indicative of future stock price performance.




**Use of Proceeds from Registered Securities**

On July 29, 2013, we completed our initial public offering ("IPO") in which we issued and sold 6,772,221 shares of our common stock, including 883,333 shares of common stock sold pursuant to the underwriters' full exercise of their option to purchase additional shares, at a public offering price of $18.00 per share, for aggregate gross proceeds of $121.9 million. All of the shares issued and sold in the IPO were registered under the Securities Act pursuant to a Registration Statement on Form S-1 (File No. 333-189216), which was declared effective by the SEC on July 23, 2013, and a Registration Statement on Form S-1 MEF (File No. 333-190091) filed pursuant to Rule 462(b) of the Securities Act. J.P. Morgan Securities LLC and Goldman, Sachs & Co. acted as joint-book-running managers of the IPO and as representatives of the underwriters. Cowen and Company, LLC and Leerink Swann LLC acted as co-managers for the IPO. The offering commenced on July 23, 2013 and did not terminate until the sale of all of the shares offered.

The net offering proceeds to us, after deducting underwriting discounts of $8.5 million and offering expenses payable by us totaling $2.4 million, were $111.0 million. No offering expenses were paid directly or indirectly to any of our directors or officers (or their associates) or persons owning 10.0% or more of any class of our equity securities or to any other affiliates. As of December 31, 2014, we have used all of the net offering proceeds primarily to fund the costs of phase 1 clinical development of AG-221, AG-120, and AG-348, to fund research and development to advance our pipeline of earlier-stage cancer metabolism and RGD programs and for working capital and general corporate purposes. Our use of the net offering proceeds is consistent with the use of proceeds described in our prospectus filed with the SEC pursuant to Rule 424(b)(4) on July 24, 2013, or the prospectus.

**Recent Sales of Unregistered Securities**

None.

**Purchases of Equity Securities by the Issuer or Affiliated Purchasers**

We did not purchase any of our registered equity securities during the period covered by this Annual Report on Form 10-K.

**Item 6. Selected Consolidated Financial Data**

You should read the following selected consolidated financial data together with our consolidated financial statements and the related notes appearing at the end of this Annual Report on Form 10-K and item 7 "Management's Discussion and Analysis of Financial Condition and Results of Operations" of this Annual Report on Form 10-K. We have derived the consolidated statements of operations data for the years ended December 31, 2014, 2013, and 2012 and the consolidated balance sheet data as of December 31, 2014 and 2013 from our audited consolidated financial statements included in this Annual Report on Form 10-K. We have derived the statement of operations data for the year ended December 31, 2011 and the consolidated balance sheet data as of December 31, 2012 and 2011 from our audited consolidated financial statements not included in this Annual report on Form 10-K. Our historical results for any prior period are not necessarily indicative of results to be expected in any future period.

| | Year Ended December 31, | | | |
|---|---|---|---|---|
| **(in thousands, except share and per share amounts)** | **2014** | **2013** | **2012** | **2011** |
| **Consolidated statements of operations:** | | | | |
| Revenues (1) | $ 65,358 | $ 25,548 | $ 25,106 | $ 21,837 |
| Operating expenses: | | | | |
| Research and development | 100,371 | 54,502 | 41,037 | 31,253 |
| General and administrative | 19,120 | 9,929 | 7,064 | 7,215 |
| Total operating expenses | 119,491 | 64,431 | 48,101 | 38,468 |
| Loss from operations | (54,133) | (38,883) | (22,995) | (16,631) |
| Interest income | 203 | 55 | 69 | 132 |
| Loss before (benefit) provision for income taxes | (53,930) | (38,828) | (22,926) | (16,499) |
| (Benefit) provision for income taxes | (426) | 579 | (2,824) | 7,207 |
| Net loss | (53,504) | (39,407) | (20,102) | (23,706) |
| Cumulative preferred stock dividends | — | (4,162) | (7,190) | (3,100) |
| Net loss applicable to common stockholders | $ (53,504) | $ (43,569) | $ (27,292) | $ (26,806) |
| Net loss per share applicable to common stockholders - basic and diluted | $ (1.59) | $ (2.83) | $ (8.02) | $ (8.90) |
| Weighted-average number of common shares used in net loss per share applicable to common stockholders - basic and diluted | 33,667,024 | 15,415,373 | 3,401,719 | 3,013,366 |

(1) In July 2014, we amended our collaboration agreement which the amendment was determined to be a material modification pursuant to FASB Accounting Standards Update No. 2009-13. Refer to Item 7 "Management's Discussion and Analysis of Financial Condition and Results of Operations" for further explanation of the modification's impact on revenue.

| (in thousands) | As of December 31, 2014 | 2013 (1) | 2012 | 2011 |
|---|---|---|---|---|
| **Consolidated Balance Sheet Data:** | | | | |
| Cash, cash equivalents and marketable securities | $ 467,447 | $ 193,894 | $ 127,976 | $ 179,168 |
| Total assets | 491,904 | 201,205 | 137,008 | 194,470 |
| Total liabilities | 67,538 | 69,723 | 93,110 | 131,330 |
| Convertible preferred stock | - | - | 115,922 | 115,922 |
| Common stock | 37 | 31 | 3 | 3 |
| Additional paid-in capital | 591,334 | 244,881 | 2,012 | 1,127 |
| Accumulated deficit | (166,948) | (113,444) | (74,037) | (53,935) |
| Total stockholders' equity (deficit) | 424,366 | 131,482 | (72,024) | (52,782) |

(1) Upon closing of our IPO in July 2013, all outstanding shares of our convertible preferred stock were converted into 19.7 million shares of common stock

## Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations

*You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and the related notes and other financial information included elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. You should review the "Risk factors" section of this Annual Report on Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.*

### Overview

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

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

Under the terms of the original agreement, we lead research, preclinical and early development efforts through phase 1, while Celgene receives an option to obtain exclusive rights either upon IND acceptance or at the end of phase 1, to further develop and commercialize medicines emerging from our cancer metabolism research. 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 rights in the United States for development candidates for which we exercise our option to retain a split license. On all programs, we are eligible to receive up to $120 million in milestone-based payments as well as royalties on any sales.

AG-221 and AG-120 are two drug candidates that have been nominated to date during the discovery phase of the collaboration. In June 2014, Celgene exercised its exclusive option to license AG-221 and gained worldwide development and commercialization rights for AG-221. We continue to conduct early clinical development activities within the AG-221 development program. We are also collaborating with Celgene on the development of AG-120. We retain U.S. development and commercialization rights for AG-120, and Celgene has an exclusive option to development and commercialization rights outside the United States. In January 2015, Celgene agreed to exercise it 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.

Since inception, our operations have focused on organizing and staffing our company, business planning, raising capital, assembling our core capabilities in cellular metabolism, identifying potential product candidates, undertaking preclinical studies and conducting clinical trials. To date, we have financed our operations primarily through funding received from our collaboration agreement with Celgene, private placements of our preferred stock, the initial public offering, or IPO, of our common stock and concurrent private placement of common stock to an affiliate of Celgene and our follow-on public offerings. Substantially all of our revenue to date has been collaboration revenue with Celgene. In connection with the IPO, our Board of Directors and stockholders approved a 1-for-2.75 reverse stock split of our common stock. The reverse stock split became effective on July 11, 2013. All share and per share amounts in the consolidated financial statements have been retroactively adjusted for all periods presented to give effect to this reverse stock split, including reclassifying an amount equal to the reduction in par value of common stock to additional paid-in capital.

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 expect to continue to incur significant expenses and operating losses over the next several years. Our net losses may fluctuate significantly from year to year. We anticipate that our expenses will increase significantly as we continue to advance and expand clinical development activities for our lead programs, AG-221, AG-120 and AG-348; continue to discover and validate novel targets and drug product candidates; expand and protect our intellectual property portfolio; hire additional commercial, development and scientific personnel; and continue to operate as a publicly-traded company.

**Financial Operations Overview**

***Revenue***

Through December 31, 2014, we have not generated any revenue from product sales and do not expect to generate any revenue from product sales in the near future. Primarily all of our revenue to date has been derived from our collaboration with Celgene and funding from research grant agreements. Through the date of the amendment of our collaboration agreement in July 2014, we were recognizing revenue related to the upfront license fee of $121.2 million, the implied premium of $3.1 million paid on the purchase of $8.8 million of Series B convertible preferred stock, and the two $20.0 million extension payments received in October 2011 and May 2014 to extend the discovery phase until April 2015, ratably over the period over which we expected to fulfill our performance obligations, which we referred to as the performance period. As a result of an amendment to the collaboration agreement in July 2014, we were required to reevaluate the arrangement under the current revenue recognition accounting guidance. Under this guidance, the best estimate of selling price of all undelivered units of accounting was estimated and was determined to be less than the combination of future contractual consideration to be received and the remaining deferred revenue balance at the amendment date. As a result, we immediately recognized revenue on the amendment date related to the excess of total arrangement consideration over the best estimate of selling price of the undelivered elements. For the period January 1, 2014 through the amendment date, we recognized a total of $42.7 million in revenues under the previous accounting guidance and upon the modification. We recognized total revenues of $65.4 million in connection with the Celgene collaboration during the year ended December 31, 2014. 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.

We expect to receive additional consideration under our collaboration agreement with Celgene related to certain development services to be performed. We will also receive an additional $20.0 million extension payment as a result of Celgene electing to extend the discovery phase until April 2016. We may also receive future milestone or royalty payments under the Celgene collaboration agreement. We expect that any revenue we generate from our collaboration agreement will fluctuate from quarter to quarter as a result of our analysis of each unit of accounting, primarily from the timing of revenue recognition related to the delivery of the license for AG-120, and the uncertain timing and amount of milestone payments, royalties and other payments.

In the future, we will seek to generate revenue from a combination of product sales and upfront payments, extension payments, cost reimbursements, milestone payments, and royalties on future product sales in connection with our Celgene collaboration or other strategic relationships.

***Research and development expenses***

Research and development expenses consist primarily of costs incurred for our research activities, including our drug discovery efforts, and the development of our product candidates, which include:

- employee-related expenses including salaries, benefits, and stock-based compensation expense;
- expenses incurred under agreements with third parties, including contract research organizations, or CROs, that conduct research and development and both preclinical and clinical activities on our behalf and the cost of consultants;
- the cost of lab supplies and acquiring, developing, and manufacturing preclinical and clinical study materials; and
- facilities, depreciation, and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance, and other operating costs.

Research and development costs are expensed as incurred. Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are deferred and capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

The following summarizes our most advanced current research and development programs.

***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. We have been evaluating AG-221 in several phase 1b dose escalation trials evaluating both hematological and solid tumor cancers with IDH2 mutations. To date, all clinical data reported by us highlights that the mechanism of response is consistent with preclinical studies, including substantial reduction of plasma 2HG levels, as well as evidence of cellular differentiation and normalization of cell counts in the bone marrow and blood. This differentiation effect is distinct from that seen with traditional chemotherapeutics commonly used to treat AML. We intend to begin a global registration program for AG-221 in 2015 for IDH2-mutant positive hematologic malignancies. In June 2014, Celgene exercised its option to an exclusive global license for development and commercialization of AG-221and is responsible for all development and commercialization costs.

***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. The clinical data reported by us highlights that the mechanism of response is consistent with the early clinical data observed in our AG-221 program and preclinical studies, including substantial reduction of plasma 2HG levels, as well as evidence of cellular differentiation and normalization of cell counts in the bone marrow and blood. This differentiation effect is distinct from that seen with traditional chemotherapeutics commonly used to treat AML. 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 it 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 U.S. 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 for AG-120, and we and Celgene would equally fund the global development costs of AG-120 that are not specific to any particular region or country. Celgene would be responsible for development and commercialization costs specific to countries outside the United States, and we would be responsible for development and commercialization costs specific to the United States. Celgene would be eligible to receive royalties on any net sales in the U.S. We would be eligible to receive royalties on any net sales outside the U.S. and up to $120.0 million in payments on achievement of certain milestones.

***AG-348: lead pyruvate kinase deficiency program***

Our lead RGD program relates to certain genetic defects of the pyruvate kinase enzyme causing a form of hemolytic anemia known as pyruvate kinase deficiency, or PK deficiency. AG-348 is an orally available, potent small molecule activator of the PKR enzyme, an isoform of PK that when mutated leads to PK deficiency, making AG-348 a highly targeted therapeutic candidate for the treatment of patients with PK deficiency.

In April 2014, we initiated a single ascending dose, or SAD, escalation phase 1 clinical trial for AG-348 in healthy volunteers and in June 2014, we initiated a multiple ascending dose, or MAD, escalation phase 1 clinical trial for healthy volunteers. The SAD trial is complete and met its primary endpoint. The MAD trial also met its primary endpoint, and recently completed dosing. The primary endpoint was to identify a safe and pharmacodynamically active dose and schedule for AG-348 to be used in subsequent clinical studies in patients with pyruvate kinase deficiency. In December 2014, we reported first clinical data from the phase 1 SAD and MAD clinical trials of AG-348. These results provided early proof-of-mechanism for AG-348 as a novel, first-in-class, oral activator of both wild-type (normal) and mutated PKR enzymes. 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.

***Other research and platform programs***

Other research and platform programs include activities related to exploratory efforts, target validation, lead optimization for our discovery and follow-on programs and our proprietary metabolomics platform.

We use our employee and infrastructure resources across multiple research and development programs, and we allocate internal employee-related and infrastructure costs, as well as certain third-party costs, to each of these programs based on the personnel resources allocated to such program. Our research and development expenses, by major program, are outlined in the table below:

| | For the years ended December 31, | | |
|---|---|---|---|
| **(in thousands)** | **2014** | **2013** | **2012** |
| IDH2 (AG-221) | $ 23,455 | $ 10,041 | $ 9,418 |
| IDH1 (AG-120) | 23,603 | 11,573 | 10,785 |
| PK deficiency (AG-348) | 16,075 | 6,892 | 5,005 |
| Other research and platform programs | 37,238 | 25,996 | 15,829 |
| Total research and development expenses | $ 100,371 | $ 54,502 | $ 41,037 |

The successful development of our product candidates is highly uncertain. As such, at this time, we cannot reasonably estimate or know the nature, timing and estimated costs of the efforts that will be necessary to complete the remainder of the development of these product candidates. We are also unable to predict when, if ever, material net cash inflows will commence from AG-221, AG-120, AG-348, or any of our other product candidates. This is due to the numerous risks and uncertainties associated with developing medicines, including the uncertainty of:

- establishing an appropriate safety profile with IND-enabling toxicology studies;
- 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 regulatory exclusivity for our product candidates;
- launching commercial sales of the products, if and when approved, whether alone or in collaboration with others; and
- maintaining an acceptable safety profile of the products following approval.

A change in the outcome of any of these variables with respect to the development of any of our product candidates would significantly change the costs and timing associated with the development of that product candidate.

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect research and development costs to increase significantly for the foreseeable future as our product candidate development programs progress. However, we do not believe that it is possible at this time to accurately project total program-specific expenses through commercialization. There are numerous factors associated with the successful commercialization of any of our product candidates, including future trial design and various regulatory requirements, many of which cannot be determined with accuracy at this time based on our stage of development. Additionally, future commercial and regulatory factors beyond our control will impact our clinical development programs and plans.

***General and administrative expenses***

General and administrative expenses consist primarily of salaries and other related costs, including stock-based compensation, for personnel in executive, finance, accounting, business development, legal and human resources functions. Other significant costs include facility costs not otherwise included in research and development expenses, legal fees relating to patent and corporate matters and fees for accounting and consulting services.

We anticipate that our general and administrative expenses will increase in the future to support continued research and development activities, potential commercialization of our product candidates and increased costs of operating as a public company. These increases will likely include increased costs related to the hiring of additional personnel and fees to outside consultants, lawyers and accountants, among other expenses. Additionally, we anticipate increased costs associated with being a public company including expenses related to services associated with maintaining compliance with exchange listing and Securities and Exchange Commission requirements, insurance, and investor relations costs.

***Interest income***

Interest income consists of interest earned on our cash and cash equivalents and available-for-sale securities.

**Critical Accounting Policies and Significant Judgments and Estimates**

Our management's discussion and analysis of our financial condition and results of operations are based on our consolidated financial statements, which we have prepared in accordance with accounting principles generally accepted in the United States. The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported amounts of revenues and expenses during the reporting periods. On an ongoing basis, we evaluate our estimates and judgments, including those described in greater detail below. We base our estimates on historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in the notes to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K, we believe that the following accounting policies are the most critical to aid you in fully understanding and evaluating our financial condition and results of operations.

***Revenue recognition***

We recognize revenue in accordance with the Financial Accounting Standards Board's (FASB) Accounting Standards Codification (ASC) 605, *Revenue Recognition*. Accordingly, revenue is recognized for each unit of accounting when all of the following criteria are met:

- persuasive evidence of an arrangement exists;
- delivery has occurred or services have been rendered;
- the seller's price to the buyer is fixed or determinable; and
- collectability is reasonably assured.

Our revenue to date has primarily been generated from a Discovery and Development Collaboration and License Agreement with Celgene (the Celgene Agreement) and from research grant agreements.

*Collaboration and License Revenue*

In January 2011, we adopted the FASB Accounting Standards Update (ASU) No. 2009-13, *Multiple-Element Revenue Arrangements (ASU No. 2009-13)*, on a prospective basis for all revenue arrangements entered into or materially modified after the adoption date. The Celgene Agreement was entered into prior to January 1, 2011 and we initially applied our pre-2011 accounting policy with respect to the arrangement. Under this policy, when evaluating multiple element arrangements, we considered whether the components of the arrangement should be accounted for individually as separate units of accounting based on whether (1) the elements have stand-alone value, and (2) we are able to estimate the fair value of all undelivered elements under the arrangement.

In July 2014, we amended our collaboration agreement with Celgene. As a result of the amendment, we were required to reevaluate the agreement under ASU No. 2009-13. The amendment was determined to be a material modification pursuant to ASU No. 2009-13, and we began recognizing revenue for the arrangement under this guidance on a prospective basis, as discussed further in Note 3 to our consolidated financial statements appearing elsewhere in this Annual Report.

Pursuant to ASU 2009-13, revenue arrangements where multiple products or services are sold together are evaluated to determine if each deliverable represents a separate unit of accounting based on the following criteria:

- Delivered item or items have value to the customer on a standalone basis, and

- If the arrangement includes a general right of return relative to the delivered item or items, delivery or performance of the undelivered item or items is considered probable and substantially in the control of the vendor.

The arrangement consideration is then allocated to each separately identified unit of accounting based on the relative selling price, using our best estimate of selling price of each deliverable. The provisions of ASC 605-25, *Multiple-Element Arrangements* are then applied to each unit of accounting to determine the appropriate revenue recognition. In the event that a deliverable of a multiple element arrangement does not represent a separate unit of accounting, we recognize revenue from the combined units of accounting over the term of the related contract or as undelivered items are delivered, as appropriate.

In determining the current and noncurrent classification of deferred revenue, we consider the total consideration expected to be earned in the next twelve months for services to be performed under certain units of accounting and the estimated proportional performance and timing of delivery of certain deliverables to determine the deferred revenue balance that will remain twelve months from the balance sheet date.

Revenue is recognized under the proportional performance method for certain units of accounting. The amount recognized is determined based on the consideration allocated to each unit of accounting based on the ratio of the level of effort incurred to date compared to the total estimated level of effort required to complete the Company's performance obligations under the unit of accounting. Determining the total estimated level of effort required to complete all performance obligations requires management judgment and estimation, including assumptions regarding future operating performance, the timelines of the clinical trials approvals and the estimated patient populations.

In January 2011, we adopted the FASB's ASU No. 2010-17, *Revenue Recognition – Milestone Method*, on a prospective basis. ASU 2010-17 provides guidance in applying the milestone method of revenue recognition to research or development arrangements. Under this guidance, management may recognize revenue contingent upon the achievement of a milestone in its entirety in the period in which the milestone is achieved, only if the milestone meets all the criteria within the guidance to be considered substantive. In accordance with ASU 2010-17, at the inception of each arrangement that includes milestone payments, we evaluate each contingent payment on an individual basis to determine whether they are considered substantive milestones, specifically reviewing factors such as the degree of certainty in achieving the milestone, the research and development risk and other risks that must be overcome to achieve the milestone, as well as the level of effort and investment required and whether the milestone consideration is reasonable relative to all deliverables and payment terms in the arrangement. This evaluation includes an assessment of whether (a) the consideration is commensurate with either (1) the entity's performance to achieve the milestone, or (2) the enhancement of the value of the delivered item(s) as a result of a specific outcome resulting from the entity's performance to achieve the milestone, (b) the consideration relates solely to past performance and (c) the consideration is reasonable relative to all of the deliverables and payment terms within the arrangement.

Revenues from milestones, if they are nonrefundable and deemed substantive, are recognized upon achievement of the milestones. We recognize revenue associated with the non-substantive milestones upon achievement of the milestone if there are no undelivered elements and we have no remaining performance obligations.

Reimbursement of research and development costs by Celgene is recognized as revenue, provided we have determined that we are acting primarily as a principal in the transaction according to the provisions outlined in FASB ASC 605-45, *Revenue Recognition – Principal Agent Considerations*, the amounts are determinable and collection of the related receivable is reasonably assured.

*Grant Revenue*

Revenue related to research grant agreements is recognized as the underlying services are performed and delivered.

***Income taxes***

Income taxes are recorded in accordance with ASC 740, *Accounting for Income Taxes (ASC 740)*, which provides for deferred taxes using an asset and liability approach. We recognize deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements or tax returns. We determine our deferred tax assets and liabilities based on differences between financial reporting and tax bases of assets and liabilities, which are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. Valuation allowances are provided, if based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized.

We account for uncertain tax positions in accordance with the provisions of Topic ASC 740. When uncertain tax positions exist, we recognize the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. The determination as to whether the tax benefit will more likely than not be realized is based upon the technical merits of the tax position as well as consideration of the available facts and circumstances. As of December 31, 2014 and 2013, we do not have any significant uncertain tax positions.

***Accrued research and development expenses***

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued expenses. This process involves reviewing quotations and contracts, identifying services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. The significant estimates in our accrued research and development expenses include fees paid to CROs in connection with research and development activities for which we have not yet been invoiced.

We base our expenses related to CROs on our estimates of the services received and efforts expended pursuant to quotes and contracts with CROs that conduct research and development on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the research and development expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and could result in us reporting amounts that are too high or too low in any particular period.

***Stock-based compensation***

We account for our stock-based compensation awards in accordance with ASC Topic 718, *Compensation—Stock Compensation* (ASC 718). ASC 718 requires all share-based payments to employees, including grants of employee stock options, to be recognized in the consolidated statements of operations based on their grant date fair values. For stock options granted to employees and to members of the board of directors for their services on the board of directors, we estimate the grant date fair value of each option award using the Black-Scholes option-pricing model. The use of the Black-Scholes option-pricing model requires our management to make assumptions with respect to the expected term of the option, the expected volatility of the common stock consistent with the expected life of the option, risk-free interest rates and expected dividend yields of the common stock. For awards subject to service-based vesting conditions, we recognize stock-based compensation expense, net of estimated forfeitures, equal to the grant date fair value of stock options on a straight-line basis over the requisite service period. For awards subject to both performance and service-based vesting conditions, we recognize stock-based compensation expense using an accelerated recognition method if achievement of the performance criteria is considered probable.

Share-based payments issued to non-employees are initially recorded at their fair values, and are revalued at each reporting date and as the equity instruments vest and are recognized as expense over the related service period in accordance with the provisions of ASC Topic 505, *Equity*. For equity instruments granted to non-employees, we recognize stock-based compensation expense using an accelerated recognition method.

If factors change and different assumptions are used, our stock-based compensation expense could be materially different in the future. There have not been any material changes in our estimated fair values to date.

***Performance-Based Stock Option Grants***

Performance-based vesting criteria for stock options primarily relate to milestone events specific to our corporate goals, including but not limited to certain preclinical and clinical development milestones related to our product candidates. Stock-based compensation expense associated with these performance-based stock options is recognized if the performance condition is considered probable of achievement using management's best estimates. Stock-based compensation related to performance-based milestones deemed to have been achieved are either fully recognized or are being recognized over the remaining service period.

***Determination of the fair value of common stock on grant dates prior to our IPO***

Prior to our IPO, we granted stock options at exercise prices equal to the estimated fair value of our common stock due to the absence of an active market for our common stock. Therefore, we periodically determined the estimated per share fair value of our common stock at various dates using contemporaneous valuations performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants Practice Aid, *Valuation of Privately-Held Company Equity Securities Issued as Compensation*, also known as the Practice Aid, for financial reporting purposes.

We performed contemporaneous valuations as of October 15, 2012 and April 15, 2013. In conducting the contemporaneous valuations, we considered all objective and subjective factors that we believed to be relevant for each valuation conducted, including our best estimate of our business condition, prospects and operating performance at each valuation date. Within the contemporaneous valuations performed, a range of factors, assumptions and methodologies were used. The significant factors included:

- the lack of an active public market for our common and our preferred stock;
- the prices of shares of our preferred stock that we had sold to outside investors in arm's length transactions, and the rights, preferences and privileges of that preferred stock relative to our common stock;
- our results of operations, financial position and the status of our research and preclinical development efforts, including our IDH2 and IDH1 and PK deficiency programs;
- the material risks related to our business;
- our business strategy;
- the market performance of publicly traded companies in the life sciences and biotechnology sectors, and recently completed mergers and acquisitions of companies comparable to us;
- the likelihood of achieving a liquidity event for the holders of our common stock, such as an initial public offering or sale of the company given prevailing market conditions; and
- any recent contemporaneous valuations of our common stock prepared in accordance with methodologies outlined in the Practice Aid.

The dates of our contemporaneous valuations have not always coincided with the dates of our stock option grants. In determining the exercise prices of the stock options set forth in the table above, our board of directors considered, among other things, the most recent contemporaneous valuations of our common stock and our assessment of additional objective and subjective factors we believed were relevant as of the grant date. The additional factors considered when determining any changes in fair value between the most recent contemporaneous valuation and the grant dates included our stage of research and preclinical development, our operating and financial performance and current business conditions.

There are significant judgments and estimates inherent in the determination of the fair value of our common stock, including the contemporaneous valuations. These judgments and estimates include assumptions regarding our future operating performance, the time to completing an IPO or other liquidity event, the related company valuations associated with such events, and the determinations of the appropriate valuation methods. If we had made different assumptions, our stock-based compensation expense, net loss and net loss per share applicable to common stockholders could have been significantly different.

*Common stock valuation methodologies.* These contemporaneous valuations were prepared in accordance with the guidelines in the Practice Aid, which prescribes several valuation approaches for determining the value of an enterprise, such as the cost, market and income approaches, and various methodologies for allocating the value of an enterprise to its capital structure and specifically the common stock.

We generally used the market approach, in particular the guideline company and precedent transaction methodologies, based on inputs from comparable public companies' equity valuations and comparable acquisition transactions, to estimate the equity value of our company. Additionally, if applicable, we considered company valuations implied by arm's length transactions involving sale of our securities to independent investors, taking into consideration the various rights and preferences of the equity securities transacted.

*Methods used to allocate our enterprise value to classes of securities.* In accordance with the Practice Aid, we considered the various methods for allocating the enterprise value across our classes and series of capital stock to determine the fair value of our common stock at each valuation date. The methods we considered consisted of the following:

- *Option pricing method.* The option-pricing method, or OPM, treats common stock and preferred stock as call options on the enterprise's value, with exercise prices based on the liquidation preference of the preferred stock. Under this method, the common stock has value only if the funds available for distribution to shareholders exceed the value of the liquidation preference at the time of a liquidity event (for example, merger or sale), assuming the enterprise has funds available to make a liquidation preference meaningful and collectible by the shareholders;
- *Probability-weighted expected return method, or PWERM.* Under a PWERM, the value of the various equity securities are estimated based upon an analysis of future values for the enterprise assuming various future outcomes. Share value is based upon the probability-weighted present value of expected future investment returns, considering each of the possible future outcomes available to the enterprise, as well as the rights of each share class.

***JOBS Act***

In April 2012, the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, was enacted. Section 107 of the JOBS Act provides that an "emerging growth company," or EGC, can take advantage of the extended transition period provided in Section 7(a)(2)(B) of the Securities Act of 1933, as amended, or the Securities Act, for complying with new or revised accounting standards. Because the market value of our common stock that was held by non-affiliates as of June 30, 2014 exceeded $700 million, we no longer qualify as of January 1, 2015, as an EGC. As a result, we are now subject to certain disclosure requirements that are applicable to other public companies that were previously not applicable to us as an EGC. These requirements include:

- compliance with the auditor attestation requirements in the assessment of our internal control over financial reporting;

- compliance with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- full disclosure obligations regarding executive compensation; and
- compliance with the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved.

***Comparison of years ended December 31, 2014 and 2013***

The following table summarizes our results of operations for the years ended December 31, 2014 and 2013, together with the changes in those items in dollars and as a percentage:

| | Years ended December 31, | | | |
|---|---|---|---|---|
| **(in thousands)** | **2014** | **2013** | **Dollar change** | **% change** |
| Total revenue | $ 65,358 | $ 25,548 | $ 39,810 | 155.8% |
| Operating expenses: | | | | |
| Research and development | 100,371 | 54,502 | 45,869 | 84.2 |
| General and administrative | 19,120 | 9,929 | 9,191 | 92.6 |
| Loss from operations | (54,133) | (38,883) | (15,250) | 39.2 |
| Interest income | 203 | 55 | 148 | 269.1 |
| (Benefit) provision for income taxes | (426) | 579 | (1,005) | (173.6) |
| Net loss | $ (53,504) | $ (39,407) | $ (14,097) | 35.8% |

*Revenue.* Revenue, which is substantially comprised of collaboration revenue from Celgene, increased by $39.8 million to $65.4 million in 2014 from $25.5 million in 2013, an increase of 156%. In July 2014, we amended our agreement with Celgene which resulted in the application of new accounting guidance to the agreement. Prior to the amendment, arrangement consideration was recognized ratably over the estimated period of performance. As a result of the amendment, we were required to reevaluate the agreement under the current revenue recognition accounting guidance. Under this guidance, the best estimate of selling price of all undelivered units of accounting was estimated and determined to be less than the combination of future contractual consideration to be received and the remaining deferred revenue balance at the amendment date. As a result we immediately recognized revenue on the amendment date related to the excess of total arrangement consideration over the best estimate of selling price of undelivered elements, which fundamentally relates to previously delivered elements under the agreement, including the exclusive global license for development and commercialization of AG-221, and on-going reimbursable development costs related to AG-221 through the amendment date. For the period January 1, 2014 through the amendment date, we recognized a total of $42.7 million in revenue under the previous accounting guidance and upon the modification. We recognized $22.7 million in revenue related to the units of accounting subsequent to the modification date.

*Research and development expense.* Research and development expenses increased by $45.9 million to $100.4 million in 2014 from $54.5 million in 2013, an increase of 84%. The increase in research and development expense was attributable to an increase of $33.8 million in external services and $12.1 million in internal expenses. The increase in external services in 2014 was attributable to the following:

- approximately $16.9 million of external costs related to phase 1 clinical studies, IND-enabling preclinical studies and manufacturing activities for our lead product candidates targeting IDH1 and PK deficiency;
- approximately $11.6 million of external costs for phase 1 clinical studies and manufacturing activities for our lead product candidate targeting IDH2; and
- approximately $5.3 million of costs related to other early research and platform programs.

We incurred approximately $12.1 million of additional internal research and development expenses related to the following:

- an increase of $9.3 million in personnel costs related to an increase in our internal headcount by 30%, which includes an increase of $4.6 million for stock-based compensation expense primarily due to an increase in our stock price and our overall headcount; and
- an increase of $2.0 million for facilities and an increase of $0.8 million for research materials and other related expenses related to our expanded research efforts.

*General and administrative expense.* General and administrative expense increased by $9.2 million to $19.1 million in 2014 from $9.9 million in 2013, an increase of 93%. The increase in general and administrative expense was primarily attributable to the following:

- an increase of $5.2 million in personnel costs related to an increase in our internal headcount by 43% which includes an increase of $3.8 million for stock-based compensation expense primarily due to an increase in our stock price and our overall headcount;
- an increase of $2.1 million in professional service costs and insurance costs related to being growing company; and
- an increase of $1.9 million in certain operating expenses, including travel and facility costs.

*Interest income.* Interest income increased by $148,000 to $203,000 in 2014 from $55,000 in 2013, an increase of 269%. The increase is attributable to interest earned on the net proceeds from our IPO in July 2013 and our follow-on offerings of common stock in April 2014 and December 2014.

*(Benefit) provision for income taxes.* The (benefit) provision for income taxes increased by $1.0 million to a $0.4 million benefit in 2014 from a $0.6 million provision for income taxes in 2013. In January 2014, we paid $6.0 million as payment in full of our U.S. federal income tax liability related to the year ended December 31, 2011, including $1.5 million of interest and penalties accrued. The increase in our benefit for income taxes for the year ended December 31, 2014 was attributable to an abatement received in August 2014 from the Internal Revenue Service of $0.4 million related to penalties previously paid. For the year ended December 31, 2013, the provision for income taxes was primarily attributable to penalties and interest accrued for the non-payment of U.S. federal income taxes on the 2011 U.S. federal income tax liability.

***Comparison of years ended December 31, 2013 and 2012***

The following table summarizes our results of operations for the years ended December 31, 2013 and 2012, together with the changes in those items in dollars and as a percentage:

| | Years ended December 31, | | | |
|---|---|---|---|---|
| (in thousands) | 2013 | 2012 | Dollar change | % change |
| Total revenue | $ 25,548 | $ 25,106 | $ 442 | 1.8% |
| Operating expenses: | | | | |
| Research and development | 54,502 | 41,037 | 13,465 | 32.8 |
| General and administrative | 9,929 | 7,064 | 2,865 | 40.6 |
| Loss from operations | (38,883) | (22,995) | (15,888) | 69.1 |
| Interest income | 55 | 69 | (14) | (20.3) |
| Provision (benefit) for income taxes | 579 | (2,824) | 3,403 | (120.5) |
| Net loss | $ (39,407) | $ (20,102) | $(19,305) | 96.0% |

*Revenue.* Revenue increased by $0.4 million to $25.5 million in 2013 from $25.1 million in 2012, an increase of 2%. The increase in revenue was the result of additional revenue recognized in December 2013 associated with Celgene's election to extend the discovery phase of the collaboration agreement through April 2015.

*Research and development expense.* Research and development expense increased by $13.5 million to $54.5 million in 2013 from $41.0 million in 2012, an increase of 33%. The increase in research and development expense was primarily attributable to an increase of $7.3 million in external services and $6.2 million in internal expenses. The increase in external services in 2013 was primarily attributable to the following:

- approximately $2.7 million of costs related to external IND-enabling preclinical studies and manufacturing activities for our lead product candidates targeting IDH1 and PK deficiency;
- approximately $1.3 million for external drug discovery efforts, primarily chemistry optimization and pharmacology, for our glutaminase research program;
- approximately $0.5 million for external phase 1 clinical studies and manufacturing activities for our lead product candidate targeting IDH2; and
- approximately $2.8 million of costs related to other early research and platform programs;

We incurred approximately $6.2 million of additional internal research and development expenses related to the following:

- additional personnel costs of $3.8 million primarily from additional hires increasing our internal headcount by 14%; and
- an increase of $1.5 million for facilities and other related expenses, $0.4 million for milestone payments payable under a collaboration agreement, and $0.5 million for research materials related to our expanded research efforts.

*General and administrative expense.* General and administrative expense increased by $2.9 million to $9.9 million in 2013 from $7.0 million in 2012, an increase of 41%. The increase in general and administrative expense was primarily attributable to the following:

- additional personnel costs of $1.7 million primarily from additional hires increasing our internal headcount by 44%;
- an increase of $0.8 million in professional service costs related to being a public company
- an increase of $0.4 million certain operating expenses, including travel and facility costs.

*Interest income.* Interest income decreased by $14,000 to $55,000 in 2013 from $69,000 in 2012, a decrease of 20%, due to a decrease in the average investment balance and a decrease in interest rates earned on investments.

*Provision (benefit) for income taxes.* During 2011, a significant portion of the upfront payment received under the collaboration agreement with Celgene was recognized as revenue for tax purposes, resulting in taxable income for 2011. Accordingly, we recorded a provision for income taxes of $7.2 million for the year ended December 31, 2011. During 2012, we elected to carry back certain deferred tax assets, including our net operating losses, generated in the year ended December 31, 2012, resulting in a reduction of our U.S. federal 2011 tax liability and a benefit for income taxes of $2.8 million for the year ended December 31, 2012. For the year ended December 31, 2013, the Company's provision for income taxes was attributable to penalties and interest accrued for the non-payment of U.S. federal income taxes on the 2011 U.S. federal income tax liability.

**Liquidity and Capital Resources**

***Sources of liquidity***

Since our inception, and through December 31, 2014, we have raised net proceeds of approximately $757.6 million to fund our operations, of which approximately $181.2 million was received through upfront,

extension, and cost reimbursement payments related to our collaboration agreement with Celgene, approximately $120.0 million was received from the issuance of preferred stock, $111.0 million was received from the IPO, after deducting underwriting discounts, commissions, and expenses, approximately $12.8 million was received from the concurrent private placement of common stock to an affiliate of Celgene, $94.7 million was received through our April 2014 follow-on offering after deducting underwriting discounts, commissions and expenses, and $237.9 million was received through our December 2014 follow-on offering after deducting underwriting discounts, commissions and expenses.

In addition to our existing cash, cash equivalents and marketable securities, we are eligible to earn a significant amount of milestone payments and are entitled to cost reimbursement under our collaboration agreement with Celgene. Our ability to earn the milestone payments and cost reimbursements and the timing of earning these amounts are dependent upon the timing and outcome of our development, regulatory, and commercial activities and are uncertain at this time. Our right to payments under our collaboration agreement is our only committed potential external source of funds.

***Cash flows***

The following table provides information regarding our cash flows for the years ended December 31, 2014, 2013 and 2012:

| | Years ended December 31, | | |
|---|---|---|---|
| **(in thousands)** | **2014** | **2013** | **2012** |
| Net cash used in operating activities | $ (59,353) | $ (56,400) | $ (49,548) |
| Net cash (used in) provided by investing activities | (333,336) | (87,217) | 23,042 |
| Net cash provided by financing activities | 335,160 | 123,880 | 142 |
| Net decrease in cash and cash equivalents | $ (57,529) | $ (19,737) | $ (26,364) |

***Net cash used in operating activities***

The use of cash in all periods resulted primarily from funding our net losses adjusted for non-cash charges and changes in components of working capital. Net cash used in operating activities was $59.4 million during the year ended December 31, 2014 compared to $56.4 million during the year ended December 31, 2013. The increase in cash used in operating activities was primarily attributable to increased operating expenses which primarily relate to increases in clinical study costs due to advancements in our three lead programs, expanded facilities and increased staffing needs due to our expanding operations. In addition, we made a $6.0 million payment for our U.S. federal income tax obligations in January 2014. Our net loss for year ended December 31, 2014 was significantly reduced by approximately $40.1 million received from Celgene, a portion of which was recognized as revenue, compared to no such amounts received from Celgene in the year ended December 31, 2013. We recognized total revenue of $65.4 million in revenue related to Celgene during the year ended December 31, 2014 as compared to $25.5 million in revenue related to Celgene during the year ended December 31, 2013.

Net cash used in operating activities was $56.4 million during the year ended December 31, 2013 compared to $49.5 million during the year ended December 31, 2012. The increase in cash used in operating activities was primarily attributable to increased operating expenses which primarily relate to increases in external phase 1 clinical studies and external IND-enabling preclinical studies for our lead programs, expanded facilities and increased staffing needs due to our expanding operations. Our net loss in 2013 is partially offset by a decrease in income taxes payable of $3.8 million due to our ability to carry back certain of our deferred tax assets, including our 2013 net operating losses for U.S. federal income tax purposes.

***Net cash (used in) provided by investing activities***

Net cash used in investing activities was $333.3 million during the year ended December 31, 2014 compared to cash used in investing activities of $87.2 million during the year ended December 31, 2013. The increase in cash used in investing activities for the year ended December 31, 2014 compared to the year ended December 31, 2013

was primarily the result of higher net purchases of marketable securities using funds received from our April 2014 and December 2014 common stock offerings and an increase of $0.9 million in purchases of property and equipment.

Net cash used by investing activities was $87.2 million during the year ended December 31, 2013 compared to $23.0 million provided by investing activities during the year ended December 31, 2012. The cash used in investing activities for the year ended December 31, 2013 was primarily the net result of more purchases of marketable securities than the proceeds from maturities and sales of marketable securities, partially offset by $0.2 million in purchases of property and equipment. The cash provided by investing activities for the year ended December 31, 2012 was primarily the result of fewer purchases of marketable securities than the proceeds from maturities and sales of marketable securities, partially offset by purchases of property and equipment of $1.5 million.

***Net cash provided by financing activities***

Net cash provided by financing activities was $335.2 million during the year ended December 31, 2014 compared to $123.9 million during the year ended December 31, 2013. The cash provided by financing activities for the year ended December 31, 2014 was primarily the result of the proceeds from the April 2014 and December 2014 follow-on public offerings of our common stock, net of underwriting discounts, commissions and expenses. The cash provided by financing activities for the year ended December 31, 2013 was primarily the result of proceeds from the initial public offering, net of underwriting discounts, commissions and expenses and proceeds from the private placement.

Net cash provided by financing activities was $123.9 million during the year ended December 31, 2013 compared to $0.1 million during the year ended December 31, 2012. The cash provided by financing activities for the year ended December 31, 2013 was primarily the result of proceeds from the initial public offering, net of underwriting discounts, commissions and expenses and proceeds from the private placement, resulting in total net proceeds of $123.7 million and proceeds received from stock option exercises of $0.2 million. The cash provided in 2012 was the result of proceeds received from stock option exercises and the issuance of common and restricted stock.

***Funding requirements***

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the research, development and 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 and distribution are not the responsibility of Celgene or other collaborators. Furthermore, we expect to continue to incur additional 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 of its option in December 2014 to extend the discovery term of our agreement for an additional year and anticipated expense reimbursements under our collaboration agreement with Celgene will enable us to 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 extent to which we acquire or in-license other medicines and technologies;
- 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; and
- our ability to establish and maintain additional collaborations on favorable terms, if at all.

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.

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. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our stockholders will be diluted, and the terms of these securities may 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.

**Off-Balance Sheet Arrangements**

We did not have, during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined under applicable Securities and Exchange Commission rules.

***Contractual obligations***

The following table summarizes our significant contractual obligations as of payment due date by period at December 31, 2014:

| | Payments due by period | | | | |
|---|---|---|---|---|---|
| (in thousands) | Total | Less than 1 year | 1-3 years | 3-5 years | More than 5 years |
| Operating lease obligations(1) | $50,381 | $4,990 | $13,527 | $14,173 | $17,691 |
| License agreements(2) | 45 | 45 | — | — | — |
| Purchase obligations(3) | — | — | — | — | — |
| Total contractual cash obligations | $50,426 | $5,035 | $13,527 | $14,173 | $17,691 |

(1) Represents future minimum lease payments under our non-cancelable operating leases. The minimum lease payments above do not include any related common area maintenance charges, or real estate taxes.

(2) As discussed in Note 6 to the consolidated financial statements appearing elsewhere in this Annual Report, we have executed several agreements to license intellectual property. The license agreements require us to pay ongoing annual maintenance payments, initially totaling $45,000 per year and increasing to $70,000 per year beginning in 2016, as well as reimburse certain patent costs previously incurred by the licensors, as applicable. All such reimbursements have been paid as of December 31, 2014. The minimum annual payments are perpetual; however, we have not included license maintenance payments beyond 2015 in the contractual obligations table above because the agreements are cancelable by us at any time upon 60-90 days prior written notice to the licensor.

(3) We enter into agreements in the normal course of business with contract research organizations for clinical trials and clinical supply manufacturing and with vendors for preclinical research studies and other services and products for operating purposes. We have not included these payments in the table of contractual obligations above since the contracts are cancelable at any time by us, generally upon 30 days prior written notice to the vendor. Under these agreements, as of December 31, 2014 we are obligated to pay up to $40.2 million to these vendors.

Other than the specific payments noted in the table of contractual obligations and as described in footnotes 2 and 3 above, milestone and royalty payments associated with certain agreements have not been included in the above table of contractual obligations as we cannot reasonably estimate if or when they will occur. At this time, no milestone payments, other than the milestone payments included in the table of contractual obligations, are probable of occurrence. Possible future payments under our arrangements include the following:

- We have agreed to make milestone payments upon achieving various patent-related, clinical development, regulatory and sales-based milestones of up to $0.1 million, $1.6 million, $5.4 million and $4.2 million, respectively, to certain licensors. The license agreements also require that we remit royalties in amounts ranging from 0.5% to 2.5% based on net sales of products utilizing the licensed technology. We are also required to make payments in amounts ranging from 7.0% to 25% for non-royalty income received from any sublicense of the rights granted to us under such agreements. None of our lead product candidates utilize technology covered by these license agreements.

- In August 2012, we entered into a license agreement pursuant to which the licensor granted us a worldwide exclusive license to certain intellectual property rights for the development of diagnostic products to detect the metabolism of certain cancers. We are obligated to pay the licensor up to $100,000 in milestone payments, contingent upon the issuance of certain patents. For each product developed under the agreement we have the right to elect to develop and commercialize the product or to grant the licensor an exclusive license to develop and commercialize the product. Under the agreement, the applicable party will pay to the other party a royalty based on worldwide net sales of products. In 2014, we incurred $50,000 in patent-based milestone expenses. To date, there have been no sales of products licensed. None of our lead product candidates utilize technology covered by the license agreement.

- We entered into an agreement with a service provider to receive discounted upfront labor costs for a defined program in consideration of a milestone payment in five years from the effective date, as defined in the agreement. The milestone is dependent on us declaring a development candidate within the five-year contract term and is dependent on the origins of the development candidate. If the development candidate is derived from a new chemical class created by the service provider, the milestone will be two times the discounted upfront labor costs. If the development candidate is not derived from a new chemical class created by the service provider, the milestone will be equal to the discount on services provided to date. No milestone payment is due if no development candidate is declared within the five year period. In addition, should no development candidate be declared within three years and we remain active with the program, the service provider may at its discretion elect to request reimbursement of the discount on services provided to date and forgo the milestone payment. The election must be provided in writing within thirty days of the end of the three-year period. The accumulated discounted labor costs through December 31, 2014 are approximately $1.0 million. We

have not accrued for the accumulated discount under the reimbursement option as we currently are unable to determine the probability of a development candidate being declared within a three-year period.

- On November 10, 2009, we entered a research funding agreement whereby we received upfront grant monies to be utilized in the development and testing of brain cancer therapies in exchange for three separate $178,538 milestone payments. The milestones can be earned over a ten-year period from the agreement date and are dependent on us successfully commercializing a brain cancer therapy product. We will make separate milestone payments when we accumulate net profits of $5.0 million, $50.0 million and $250.0 million, respectively, from sales of the product. As of December 31, 2014, we have not commercialized a brain cancer therapy product.

**Item 7A. Quantitative and Qualitative Disclosures about Market Risk**

We are exposed to market risk related to changes in interest rates. As of December 31, 2014, we had cash, cash equivalents and marketable securities of $467.4 million, consisting primarily of investments in U.S. Treasuries and certificates of deposit. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are in short-term marketable securities. Our marketable securities are subject to interest rate risk and could fall in value if market interest rates increase. Due to the short-term duration of our investment portfolio and the low risk profile of our investments, we do not believe an immediate 10% change in interest rates would have a material effect on the fair market value of our investment portfolio. We have the ability to hold our marketable securities until maturity, and therefore we would not expect our operating results or cash flows to be affected to any significant degree by the effect of a change in market interest rates on our investments.

We are also exposed to market risk related to changes in foreign currency exchange rates. We have contracts with CROs that are located in Asia and Europe that are denominated in foreign currencies. We are subject to fluctuations in foreign currency rates in connection with these agreements. We do not currently hedge our foreign currency exchange rate risk. As of December 31, 2014 and December 31, 2013, we had minimal or no liabilities denominated in foreign currencies.

**Item 8. Financial Statements and Supplementary Data**

The financial statements required to be filed pursuant to this Item 8 are appended to this report. An index of those financial statements is found in Item 15 of Part IV of this Annual Report on Form 10-K.

**Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure**

None.

**Item 9A. Controls and Procedures**

**Evaluation of Disclosure Controls and Procedures**

Our management, with the participation of our principal executive officer and our principal financial officer, evaluated, as of the end of the period covered by this Annual Report on Form 10-K, the effectiveness of our disclosure controls and procedures. Based on that evaluation of our disclosure controls and procedures as of December 31, 2014, our principal executive officer and principal financial officer concluded that our disclosure controls and procedures as of such date are effective at the reasonable assurance level. The term “disclosure controls and procedures,” as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act are recorded, processed, summarized and reported within the time periods specified in the SEC’s rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by us in the reports we file or submit under the Exchange Act is accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate to allow

timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and our management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

**Management's Annual Report on Internal Control over Financial Reporting**

Our management is responsible for establishing and maintaining adequate internal control over our financial reporting. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, our principal executive and principal financial officers and effected by our board of directors, management and other personnel to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with U.S. GAAP. Our internal control over financial reporting includes those policies and procedures that:

- pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect our transactions and dispositions of our assets;
- provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with U.S. GAAP, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and
- provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our assets that could have a material effect on our financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2014. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in its 2013 Internal Control — Integrated Framework. Based on our assessment, our management has concluded that, as of December 31, 2014, our internal control over financial reporting is effective based on those criteria.

Our independent registered public accounting firm has issued an attestation report of our internal control over financial reporting. This report appears below.

**Report of Independent Registered Public Accounting Firm**

The Board of Directors and Shareholders of Agios Pharmaceuticals, Inc.

We have audited Agios Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2014, based on criteria established in the 2013 Internal Control – Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (the COSO criteria). Agios Pharmaceuticals, Inc.'s management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Annual Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit.

We conducted our audit in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about

whether effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exits, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

In our opinion, Agios Pharmaceuticals, Inc. maintained, in all material respects, effective internal control over financial reporting as of December 31, 2014 based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the consolidated balance sheets of Agios Pharmaceuticals, Inc. as of December 31, 2014 and 2013, and the related consolidated statements of operations, comprehensive loss, convertible preferred stock and stockholders' (deficit) equity, and cash flows for each of the three years in the period ended December 31, 2014 and our report dated February 24, 2015 expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

Boston, Massachusetts
February 24, 2015

**Changes in Internal Control over Financial Reporting**

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during the fiscal quarter ended December 31, 2014 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

**Item 9B. Other Information**

None.

**PART III**

**Item 10. Directors, Executive Officers and Corporate Governance**

The information required by this Item 10 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2015 Annual Meeting of Stockholders and is incorporated herein by reference.

**Item 11. Executive Compensation**

The information required by this Item 11 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2015 Annual Meeting of Stockholders and is incorporated herein by reference.

**Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters**

The information required by this Item 12 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2015 Annual Meeting of Stockholders and is incorporated herein by reference.

**Item 13. Certain Relationships and Related Transactions, and Director Independence**

The information required by this Item 13 will be included, as applicable, in our definitive proxy statement to be filed with the SEC with respect to our 2015 Annual Meeting of Stockholders and is incorporated herein by reference.

**Item 14. Principal Accounting Fees and Services**

The information required by this Item 14 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2015 Annual Meeting of Stockholders and is incorporated herein by reference.

## PART IV

### Item 15. Exhibits and Financial Statement Schedules

**(1) Financial Statements**

The following documents are included on pages F-1 through F-34 attached hereto and are filed as part of this Annual Report on Form 10-K.



**(2) Financial Statement Schedules**

Schedules have been omitted since they are either not required or not applicable or the information is otherwise included herein.

**(3) Exhibits**

The exhibits filed as part of this Annual Report on Form 10-K are listed in the Exhibit Index immediately preceding such Exhibits, which Exhibit Index is incorporated herein by reference.

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**SIGNATURES**

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Date: February 24, 2015 By: /s/ David P. Schenkein

David P. Schenkein, M.D

*President and Chief Executive Officer*

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

| Signature | Title | Date |
|---|---|---|
| /s/ David P. Schenkein<br>David P. Schenkein, M.D. | Chief Executive Officer and Director (Principal executive officer) | Date: February 24, 2015 |
| /s/ Glenn Goddard<br>Glenn Goddard | Senior Vice President, Finance (Principal financial and accounting officer) | Date: February 24, 2015 |
| /s/ Lewis C. Cantley<br>Lewis C. Cantley, Ph.D. | Director | Date: February 24, 2015 |
| /s/ Paul J. Clancy<br>Paul J. Clancy | Director | Date: February 24, 2015 |
| /s/ Douglas G. Cole<br>Douglas G. Cole, M.D. | Director | Date: February 24, 2015 |
| /s/ Kaye Foster-Cheek<br>Kaye Foster-Cheek | Director | Date: February 24, 2015 |
| /s/ Perry Karsen<br>Perry Karsen | Director | Date: February 24, 2015 |
| /s/ John M. Maraganore<br>John M. Maraganore, Ph.D. | Director | Date: February 24, 2015 |
| /s/ Robert T. Nelsen<br>Robert T. Nelsen | Director | Date: February 24, 2015 |
| /s/ Kevin P. Starr<br>Kevin P. Starr | Director | Date: February 24, 2015 |
| /s/ Marc Tessier-Lavigne<br>Marc Tessier-Lavigne, Ph.D. | Director | Date: February 24, 2015 |

Agios Pharmaceuticals, Inc.

Index to Consolidated Financial Statements

Report of Independent Registered Public Accounting Firm

The Board of Directors and Stockholders
Agios Pharmaceuticals, Inc.

We have audited the accompanying consolidated balance sheets of Agios Pharmaceuticals, Inc. (the "Company") as of December 31, 2014 and 2013, and the related consolidated statements of operations, comprehensive loss, convertible preferred stock and stockholders' (deficit) equity, and cash flows for each of the three years in the period ended December 31, 2014. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of Agios Pharmaceuticals, Inc. at December 31, 2014 and 2013, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2014, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), Agios Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2014, based on criteria established in the 2013 Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission and our report dated February 24, 2015 expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

Boston, Massachusetts
February 24, 2015

Agios Pharmaceuticals, Inc.

Consolidated Balance Sheets
(In thousands, except share and per share data)

| | December 31, | |
|---|---|---|
| | 2014 | 2013 |
| **Assets** | | |
| Current assets: | | |
| Cash and cash equivalents | $ 14,031 | $ 71,560 |
| Marketable securities | 328,034 | 95,209 |
| Collaboration receivable – related party | 6,492 | 476 |
| Other receivables | 2,334 | - |
| Prepaid expenses and other current assets | 4,814 | 2,502 |
| Refundable income taxes | 3,841 | - |
| Total current assets | 359,546 | 169,747 |
| Marketable securities | 125,382 | 27,125 |
| Property and equipment, net | 6,386 | 3,758 |
| Restricted cash | - | 571 |
| Other assets | 590 | 4 |
| Total assets | $ 491,904 | $ 201,205 |
| **Liabilities and stockholders' equity** | | |
| Current liabilities: | | |
| Accounts payable | $ 11,067 | $ 3,678 |
| Accrued expenses | 14,020 | 6,586 |
| Income taxes payable | - | 1,462 |
| Deferred revenue – related party | 35,686 | 25,072 |
| Deferred rent | 310 | 123 |
| Other current liabilities | 6 | 9 |
| Total current liabilities | 61,089 | 36,930 |
| Deferred revenue, net of current portion – related party | 2,725 | 32,567 |
| Deferred rent, net of current portion | 3,724 | 220 |
| Other non-current liabilities | - | 6 |
| Commitments and contingencies (*Note 6*) | | |
| Stockholders' equity: | | |
| Preferred stock, $0.001 par value; 25,000,000 shares authorized, no shares issued and outstanding at December 31, 2014 and 2013 | - | - |
| Common stock, $0.001 par value; 125,000,000 shares authorized and 37,100,513 and 31,202,542 shares issued and outstanding at December 31, 2014 and 2013, respectively | 37 | 31 |
| Additional paid-in capital | 591,334 | 244,881 |
| Accumulated other comprehensive (loss) income | (57) | 14 |
| Accumulated deficit | (166,948) | (113,444) |
| Total stockholders' equity | 424,366 | 131,482 |
| Total liabilities and stockholders' equity | $ 491,904 | $ 201,205 |

*See Notes to Consolidated Financial Statements.*

Agios Pharmaceuticals, Inc.

Consolidated Statements of Operations
(in thousands, except share and per share data)

| | Years Ended December 31, | | |
|---|---|---|---|
| | 2014 | 2013 | 2012 |
| Collaboration revenue – related party | $ 65,358 | $ 25,548 | $ 25,072 |
| Grant revenue | - | - | 34 |
| Total revenue | 65,358 | 25,548 | 25,106 |
| Operating expenses: | | | |
| Research and development | 100,371 | 54,502 | 41,037 |
| General and administrative | 19,120 | 9,929 | 7,064 |
| Total operating expenses | 119,491 | 64,431 | 48,101 |
| Loss from operations | (54,133) | (38,883) | (22,995) |
| Interest income | 203 | 55 | 69 |
| Loss before (benefit) provision for income taxes | (53,930) | (38,828) | (22,926) |
| (Benefit) provision for income taxes | (426) | 579 | (2,824) |
| Net loss | (53,504) | (39,407) | (20,102) |
| Cumulative preferred stock dividends | - | (4,162) | (7,190) |
| Net loss applicable to common stockholders | $ (53,504) | $ (43,569) | $ (27,292) |
| Net loss per share applicable to common stockholders – basic and diluted | $ (1.59) | $ (2.83) | $ (8.02) |
| Weighted-average number of common shares used in net loss per share applicable to common stockholders – basic and diluted | 33,667,024 | 15,415,373 | 3,401,719 |

*See Notes to Consolidated Financial Statements.*

Agios Pharmaceuticals, Inc.

Consolidated Statements of Comprehensive Loss
(in thousands)

| | Years Ended December 31, | | |
|---|---|---|---|
| | 2014 | 2013 | 2012 |
| Net loss | $ (53,504) | $ (39,407) | $ (20,102) |
| Other comprehensive (loss) income: | | | |
| Unrealized (loss) gain on available-for-sale securities | (71) | 16 | (25) |
| Comprehensive loss | $ (53,575) | $ (39,391) | $ (20,127) |

*See Notes to Consolidated Financial Statements.*

Agios Pharmaceuticals, Inc.

Consolidated Statements of Convertible Preferred Stock and Stockholders' (Deficit) Equity
(in thousands, except share amounts)

| | Series A Convertible Preferred Stock | | Series B Convertible Preferred Stock | | Series C Convertible Preferred Stock | | Common Stock | | Additional Paid-In Capital | Accumulated Other Comprehensive Income (Loss) | Accumulated Deficit | Total Stockholders' (Deficit) Equity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Shares | Amount | Shares | Amount | Shares | Amount | Shares | Amount | | | | |
| Balance at December 31, 2011 | 33,188,889 | $ 32,940 | 5,190,551 | $ 5,681 | 15,882,389 | $ 77,301 | 3,197,420 | $ 3 | $ 1,127 | $ 23 | $ (53,935) | $ (52,782) |
| Unrealized loss on marketable securities | — | — | — | — | — | — | — | — | — | (25) | — | (25) |
| Net loss | — | — | — | — | — | — | — | — | — | — | (20,102) | (20,102) |
| Stock-based compensation expense | — | — | — | — | — | — | — | — | 742 | — | — | 742 |
| Vesting of restricted stock | — | — | — | — | — | — | 183,713 | — | 56 | — | — | 56 |
| Issuance of common stock upon exercise of stock options | — | — | — | — | — | — | 234,968 | — | 87 | — | — | 87 |
| Balance at December 31, 2012 | 33,188,889 | $ 32,940 | 5,190,551 | $ 5,681 | 15,882,389 | $ 77,301 | 3,616,101 | $ 3 | $ 2,012 | $ (2) | $ (74,037) | $ (72,024) |
| Unrealized gain on marketable securities | — | — | — | — | — | — | — | — | — | 16 | — | 16 |
| Net loss | — | — | — | — | — | — | — | — | — | — | (39,407) | (39,407) |
| Stock-based compensation expense | — | — | — | — | — | — | — | — | 3,030 | — | — | 3,030 |
| Vesting of restricted stock | — | — | — | — | — | — | 136,758 | — | 64 | — | — | 64 |
| Issuance of common stock upon exercise of stock options | — | — | — | — | — | — | 237,565 | — | 150 | — | — | 150 |
| Conversion of convertible preferred stock upon initial public offering | (33,188,889) | $(32,940) | (5,190,551) | $(5,681) | (15,882,389) | $(77,301) | 19,731,564 | 20 | 115,903 | — | — | 115,923 |
| Issuance of common stock for initial public offering, net of issuance costs of $2.4 million | — | — | — | — | — | — | 6,772,221 | 7 | 110,973 | — | — | 110,980 |
| Issuance of common stock for private placement | — | — | — | — | — | — | 708,333 | 1 | 12,749 | — | — | 12,750 |
| Balance at December 31, 2013 | — | $ — | — | $ — | — | $ — | 31,202,542 | $ 31 | $ 244,881 | $ 14 | $ (113,444) | $ 131,482 |
| Unrealized loss on marketable securities | — | — | — | — | — | — | — | — | — | (71) | — | (71) |
| Net loss | — | — | — | — | — | — | — | — | — | — | (53,504) | (53,504) |
| Stock-based compensation expense | — | — | — | — | — | — | — | — | 11,506 | — | — | 11,506 |
| Vesting of restricted stock | — | — | — | — | — | — | 14,773 | — | 9 | — | — | 9 |
| Issuance of common stock upon exercise of stock options | — | — | — | — | — | — | 1,298,775 | 1 | 2,322 | — | — | 2,323 |
| Issuance of common stock for follow-on offerings, net of issuance costs of $0.9 million | — | — | — | — | — | — | 4,584,423 | 5 | 332,616 | — | — | 332,621 |
| Balance at December 31, 2014 | — | $ — | — | $ — | — | $ — | 37,100,513 | $ 37 | $ 591,334 | $ (57) | $ (166,948) | $ 424,366 |

*See Notes to Consolidated Financial Statements.*

Agios Pharmaceuticals, Inc.

Consolidated Statements of Cash Flows
(in thousands)

| | Years Ended December 31, | | |
|---|---|---|---|
| | 2014 | 2013 | 2012 |
| **Operating activities** | | | |
| Net loss | $ (53,504) | $ (39,407) | $ (20,102) |
| Adjustments to reconcile net loss to net cash used in operating activities: | | | |
| Depreciation | 1,367 | 1,440 | 1,179 |
| Net loss on disposal of fixed assets | — | — | 10 |
| Stock-based compensation expense | 11,506 | 3,030 | 742 |
| Deferred taxes | — | 3,842 | 6,707 |
| Net amortization of premiums and discounts on investments | 538 | 284 | 287 |
| Changes in operating assets and liabilities: | | | |
| Collaboration receivable – related party | (6,016) | (476) | — |
| Other receivables | (2,334) | — | — |
| Prepaid expenses and other assets | (2,878) | (1,562) | (94) |
| Accounts payable | 7,577 | 30 | (322) |
| Accrued expenses and other liabilities | 5,231 | 4,878 | 156 |
| Deferred rent | 3,691 | (85) | (46) |
| Refundable income taxes and income taxes payable | (5,303) | (3,302) | (12,993) |
| Deferred revenue – related party | (19,228) | (25,072) | (25,072) |
| Net cash used in operating activities | (59,353) | (56,400) | (49,548) |
| **Investing activities** | | | |
| Purchases of marketable securities | (837,219) | (146,049) | (88,524) |
| Proceeds from maturities and sales of marketable securities | 505,528 | 60,126 | 113,041 |
| Purchases of property and equipment | (2,216) | (1,294) | (1,475) |
| Release of restricted cash | 571 | — | — |
| Net cash (used in) provided by investing activities | (333,336) | (87,217) | 23,042 |
| **Financing activities** | | | |
| Proceeds from public offering of common stock, net of commissions | 333,577 | 113,367 | — |
| Proceeds from private placement | — | 12,750 | — |
| Payment of public offering costs | (720) | (2,387) | — |
| Net proceeds from stock option exercises and issuance of common and restricted common stock | 2,303 | 150 | 142 |
| Net cash provided by financing activities | 335,160 | 123,880 | 142 |
| Net decrease in cash and cash equivalents | (57,529) | (19,737) | (26,364) |
| Cash and cash equivalents at beginning of the period | 71,560 | 91,297 | 117,661 |
| Cash and cash equivalents at end of the period | $ 14,031 | $ 71,560 | $ 91,297 |
| **Supplemental cash flow information** | | | |
| Cash paid for income taxes | $ 5,980 | $ — | $ 3,549 |
| **Supplemental disclosure of non-cash investing and financing transactions:** | | | |
| Conversion of convertible preferred stock upon initial public offering | $ — | $ 115,923 | $ — |
| Vesting of restricted stock | $ 9 | $ 64 | $ — |
| Additions to property, plant and equipment included in accounts payable and accrued expenses | $ 2,118 | $ 339 | $ 57 |
| Proceeds from stock option exercises in other current assets | $ 20 | $ — | $ — |
| Public offering costs in accounts payable and accrued expenses | $ 236 | $ — | $ — |

*See Notes to Consolidated Financial Statements.*

Agios Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements

**1. Nature of Business**

Agios Pharmaceuticals, Inc. ("Agios" or "the Company") is a biopharmaceutical company committed to the fundamental transformation of patients' lives through scientific leadership in the field of cancer metabolism and rare genetic disorders of metabolism. The Company has built a unique set of core capabilities in the field of cellular metabolism, with the goal of making transformative, first or best in class medicines. The Company's therapeutic areas of focus are cancer and rare genetic disorders of metabolism, which are a broad group of more than 600 rare genetic diseases caused by mutations, or defects, of single metabolic genes. In both of these areas, the Company is seeking to unlock the biology of cellular metabolism to create transformative therapies. The Company is located in Cambridge, Massachusetts.

***Liquidity***

The Company has an accumulated deficit as of December 31, 2014 of $166.9 million and will require substantial capital for research and product development. The future success of the Company is dependent on its ability to develop its product candidates and ultimately upon its ability to attain profitable operations. The Company is subject to a number of risks similar to other life science companies, including, but not limited to, risks related to the successful discovery and development of its drug candidates, raising additional capital, development of new technological innovations by its competitors, protection of proprietary technology, and market acceptance of the Company's products.

On July 29, 2013, the Company closed an initial public offering ("IPO") of its common stock, which resulted in the sale of 6,772,221 shares of its common stock at a public offering price of $18.00 per share, including 883,333 shares of common stock issued upon the exercise in full by the underwriters of their option to purchase additional shares at the public offering price to cover over-allotments. The Company received net proceeds from the IPO of $111.0 million, after deducting underwriting discounts, commissions and expenses payable by the Company. Additionally, an affiliate of Celgene Corporation ("Celgene"), the Company's cancer metabolism strategic alliance partner, purchased 708,333 shares of common stock in a separate private placement concurrent with the completion of the IPO at a purchase price of $18.00 per share for aggregate proceeds of $12.8 million.

In April 2014, the Company completed a public offering of 2,000,000 shares of its common stock at a public offering price of $44.00 per share. The Company received net proceeds from this offering of $82.3 million, after deducting underwriting discounts, commissions and expenses payable by the Company. Celgene purchased 294,800 shares of the Company's common stock in the offering. In addition, the Company granted the underwriters the right to purchase up to an additional 300,000 shares of its common stock which was exercised in May 2014 resulting in additional net proceeds to the Company of $12.4 million, after underwriting discounts and commissions paid by the Company.

In December 2014, the Company completed a public offering of 1,986,455 shares of its common stock at a public offering price of $110.75 per share. The Company received net proceeds from this offering of $206.9 million, after deducting underwriting discounts, commissions and expenses payable by the Company. In addition, the Company granted the underwriters the right to purchase up to an additional 297,968 shares of its common stock which was exercised in December 2014 resulting in additional net proceeds to the Company of $31.0 million, after underwriting discounts and commissions paid by the Company.

In addition to the Company's existing cash, cash equivalents and marketable securities, the Company is eligible to earn a significant amount of milestone payments, an additional extension payment of $20.0 million and is entitled to additional cost reimbursements under its collaboration agreement with Celgene. At December 31, 2014, the Company believes its cash, cash equivalents and marketable securities, totaling $467.4 million, are sufficient to fund operations for a period of at least 12 months from the balance sheet date.

**2. Summary of Significant Accounting Policies**

***Principles of Consolidation***

The Company's consolidated financial statements include the Company's accounts and the accounts of the Company's wholly owned subsidiary, Agios Securities Corporation. All intercompany transactions have been eliminated in consolidation. The consolidated financial statements have been prepared in conformity with U.S. generally accepted accounting principles ("GAAP").

***Use of Estimates***

The preparation of financial statements in conformity with U.S. GAAP requires the Company's management to make estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenue and expenses during the reporting period. The Company bases its estimates on historical experience and on various other assumptions that are believed to be reasonable under the circumstances. Actual results could differ from those estimates.

Prior to the IPO, the Company utilized significant estimates and assumptions in determining the fair value of its common stock. The board of directors determined the estimated fair value of the Company's common stock based on a number of objective and subjective factors, including external market conditions affecting the biotechnology industry sector and the prices at which the Company sold shares of convertible preferred stock, the superior rights and preferences of securities senior to the Company's common stock at the time and the likelihood of achieving a liquidity event, such as an initial public offering or sale of the Company. The Company utilized various valuation methodologies in accordance with the framework of the American Institute of Certified Public Accountants, or AICPA, *Audit and Accounting Practice Aid Series: Valuation of Privately Held Company Equity Securities Issued as Compensation*, or the AICPA Practice Aid, to estimate the fair value of its common stock and in performing retrospective valuation analyses for certain grant dates prior to the IPO. The methodologies included the option pricing method utilizing the back-solve method (a form of the market approach defined in the AICPA Practice Aid) and the probability-weighted expected return method based upon the probability of occurrence of certain future liquidity events such as an initial public offering or sale of the Company. Each valuation methodology included estimates and assumptions that require the Company's judgment. Significant changes to the key assumptions used in the valuations could result in different fair values of common stock at each valuation date.

***Revenue Recognition***

The Company recognizes revenue in accordance with the Financial Accounting Standards Board's ("FASB") Accounting Standards Codification ("ASC") 605, *Revenue Recognition*. Accordingly, revenue is recognized for each unit of accounting when all of the following criteria are met:

- persuasive evidence of an arrangement exists;
- delivery has occurred or services have been rendered;
- the seller's price to the buyer is fixed or determinable; and
- collectability is reasonably assured.

The Company's revenue has primarily been generated from a Discovery and Development Collaboration and License Agreement with Celgene ("the Celgene Agreement") and from research grant agreements.

*Collaboration and License Revenue*

In January 2011, the Company adopted the FASB Accounting Standards Update ("ASU") No. 2009-13, *Multiple-Element Revenue Arrangements* ("ASU No. 2009-13"), on a prospective basis for all revenue arrangements entered into or materially modified after the adoption date. The Celgene Agreement was entered into prior to January 1, 2011 and the Company initially applied its prior accounting policy with respect to the arrangement. Under this policy, when evaluating multiple element arrangements, the Company considered whether the components of the arrangement should be accounted for individually as separate units of accounting if (1) the elements have stand-alone value, and (2) the Company is able to estimate the fair value of all undelivered elements under the arrangement.

In July 2014, the Company amended its collaboration agreement with Celgene. As a result of the amendment, the Company was required to reevaluate the agreement under ASU No. 2009-13. The amendment was determined to be a material modification pursuant to ASU No. 2009-13, and the Company began recognizing revenue for the arrangement under this guidance on a prospective basis, as discussed further in Note 3.

Pursuant to ASU 2009-13, revenue arrangements where multiple products or services are sold together are evaluated to determine if each deliverable represents a separate unit of accounting based on the following criteria:

- Delivered item or items have value to the customer on a standalone basis, and
- If the arrangement includes a general right of return relative to the delivered item or items, delivery or performance of the undelivered item or items is considered probable and substantially in the control of the vendor.

The arrangement consideration is then allocated to each separately identified unit of accounting based on the relative selling price, using the Company's best estimate of selling price of each deliverable. The provisions of ASC 605-25, *Multiple-Element Arrangements* are then applied to each unit of accounting to determine the appropriate revenue recognition. In the event that a deliverable of a multiple element arrangement does not represent a separate unit of accounting, the Company recognizes revenue from the combined units of accounting over the term of the related contract or as undelivered items are delivered, as appropriate.

In determining the current and noncurrent classification of deferred revenue, the Company considers the total consideration expected to be earned in the next twelve months for services to be performed under certain units of accounting and the estimated proportional performance and timing of delivery of certain deliverables to determine the deferred revenue balance that will remain twelve months from the balance sheet date.

Revenue is recognized under the proportional performance method for certain units of accounting. The amount recognized is determined based on the consideration allocated to each unit of accounting based on the ratio of the level of effort incurred to date compared to the total estimated level of effort required to complete the Company's performance obligations under the unit of accounting. Determining the total estimated level of effort required to complete all performance obligations requires management judgment and estimation, including assumptions regarding future operating performance, the timelines of the clinical trials approvals and the estimated patient populations.

In January 2011, the Company adopted the FASB's ASU No. 2010-17, *Revenue Recognition – Milestone Method*, on a prospective basis. ASU 2010-17 provides guidance in applying the milestone method of revenue recognition to research or development arrangements. Under this guidance, management may recognize revenue contingent upon the achievement of a milestone in its entirety in the period in which the milestone is achieved, only if the milestone meets all the criteria within the guidance to be considered substantive. In accordance with ASU 2010-17, at the inception of each arrangement that includes milestone payments, the Company evaluates each contingent payment on an individual basis to determine whether they are considered substantive milestones,

specifically reviewing factors such as the degree of certainty in achieving the milestone, the research and development risk and other risks that must be overcome to achieve the milestone, as well as the level of effort and investment required and whether the milestone consideration is reasonable relative to all deliverables and payment terms in the arrangement. This evaluation includes an assessment of whether (a) the consideration is commensurate with either (1) the entity's performance to achieve the milestone, or (2) the enhancement of the value of the delivered item(s) as a result of a specific outcome resulting from the entity's performance to achieve the milestone, (b) the consideration relates solely to past performance and (c) the consideration is reasonable relative to all of the deliverables and payment terms within the arrangement.

Revenues from milestones, if they are nonrefundable and deemed substantive, are recognized upon achievement of the milestones. The Company recognizes revenue associated with the non-substantive milestones upon achievement of the milestone if there are no undelivered elements and the Company has no remaining performance obligations.

Reimbursement of research and development costs by Celgene is recognized as revenue, provided the Company has determined that it is acting primarily as a principal in the transaction according to the provisions outlined in FASB ASC 605-45, *Revenue Recognition – Principal Agent Considerations*, the amounts are determinable and collection of the related receivable is reasonably assured.

*Grant Revenue*

Revenue related to research grant agreements is recognized as the underlying services are performed and delivered. Revenues from grants totaled approximately $0.1 million for the year ended December 31, 2012. The Company did not recognize any grant revenue for the years ended December 31, 2014 and 2013.

***Research and Development Costs***

Research and development costs are expensed as incurred. Research and development costs include salaries and personnel-related costs, consulting fees, fees paid for contract research services, fees paid to clinical research organizations and other third parties associated with clinical trials, the costs of laboratory equipment and facilities, and other external costs.

Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are deferred and capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

***Stock-Based Compensation***

The Company accounts for its stock-based compensation awards in accordance with ASC Topic 718, *Compensation – Stock Compensation* ("ASC 718"). ASC 718 requires all share-based payments to employees, including grants of employee stock options, to be recognized in the consolidated statements of operations based on their grant date fair values. For stock options granted to employees and to members of the board of directors for their services on the board of directors, the Company estimates the grant date fair value of each option award using the Black-Scholes option-pricing model. The use of the Black-Scholes option-pricing model requires management to make assumptions with respect to the expected term of the option, the expected volatility of the common stock consistent with the expected life of the option, risk-free interest rates and expected dividend yields of the common stock. For awards subject to service-based vesting conditions, the Company recognizes stock-based compensation expense, net of estimated forfeitures, equal to the grant date fair value of stock options on a

straight-line basis over the requisite service period. For awards subject to both performance and service-based vesting conditions, the Company recognizes stock-based compensation expense using an accelerated recognition method if achievement of the performance criteria is considered probable.

Share-based payments issued to non-employees are recorded at their fair values, and are revalued at each reporting date and as the equity instruments vest and are recognized as expense over the related service period in accordance with the provisions of ASC Topic 505, *Equity*. For equity instruments granted to non-employees, the Company recognizes stock-based compensation expense using an accelerated recognition method.

During the years ended December 31, 2014, 2013, and 2012, the Company recorded stock-based compensation expense for employee and non-employee stock options, the employee stock purchase plan and restricted stock, which was allocated as follows in the consolidated statements of operations (in thousands):

| | Years Ended December 31, | | |
|---|---|---|---|
| | 2014 | 2013 | 2012 |
| Research and development expense | $ 6,688 | $ 2,001 | $ 605 |
| General and administrative expense | 4,818 | 1,029 | 137 |
| | $ 11,506 | $ 3,030 | $ 742 |

No related tax benefits were recognized for the years ended December 31, 2014, 2013 and 2012.

***Income Taxes***

Income taxes are recorded in accordance with ASC 740, *Accounting for Income Taxes ("ASC 740")*, which provides for deferred taxes using an asset and liability approach. The Company recognizes deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements or tax returns. The Company determines its deferred tax assets and liabilities based on differences between financial reporting and tax bases of assets and liabilities, which are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. Valuation allowances are provided, if based upon the weight of available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized.

The Company accounts for uncertain tax positions in accordance with the provisions of ASC 740. When uncertain tax positions exist, the Company recognizes the tax benefit of tax positions to the extent that the benefit will more likely than not be realized. The determination as to whether the tax benefit will more likely than not be realized is based upon the technical merits of the tax position as well as consideration of the available facts and circumstances. As of December 31, 2014 and 2013, the Company did not have any uncertain tax positions.

***Comprehensive Income (Loss)***

Comprehensive income (loss) is defined as the change in equity of a business enterprise during a period from transactions, and other events and circumstances from non-owner sources, and currently consists of net loss and changes in unrealized gains and losses on available-for-sale securities. Accumulated other comprehensive loss consists entirely of unrealized gains and losses from available for sale securities as of December 31, 2014 and 2013.

***Cash and Cash Equivalents***

The Company considers highly liquid investments with a maturity of ninety days or less when purchased to be cash equivalents. Cash equivalents, which consist primarily of money market funds, are stated at fair value.

***Marketable Securities***

Marketable securities at December 31, 2014 and 2013 consisted primarily of investments in United States Treasuries and certificates of deposit. Management determines the appropriate classification of the securities at the time they are acquired and evaluates the appropriateness of such classifications at each balance sheet date. The Company classifies its marketable securities as available-for-sale pursuant to ASC 320, *Investments – Debt and Equity Securities*. Marketable securities are recorded at fair value, with unrealized gains and losses included as a component of accumulated other comprehensive income (loss) in stockholders' equity and a component of total comprehensive loss in the consolidated statements of comprehensive loss, until realized. The fair value of these securities is based on quoted prices for identical or similar assets. Realized gains and losses are included in investment income on a specific-identification basis. There were no realized gains or losses on marketable securities for the years ended December 31, 2014, 2013 and 2012.

The Company reviews marketable securities for other-than-temporary impairment whenever the fair value of a marketable security is less than the amortized cost and evidence indicates that a marketable security's carrying amount is not recoverable within a reasonable period of time. Other-than-temporary impairments of investments are recognized in the consolidated statements of operations if the Company has experienced a credit loss, has the intent to sell the marketable security, or if it is more likely than not that the Company will be required to sell the marketable security before recovery of the amortized cost basis. Evidence considered in this assessment includes reasons for the impairment, compliance with the Company's investment policy, the severity and the duration of the impairment and changes in value subsequent to the end of the period.

Marketable securities at December 31, 2014 consist of the following (in thousands):

| | Amortized Cost | Unrealized Gains | Unrealized Losses | Fair Value |
|---|---|---|---|---|
| Current: | | | | |
| Certificates of deposit | $ 13,160 | $ — | $ (5) | $ 13,155 |
| U.S. Treasuries | 314,866 | 45 | (32) | 314,879 |
| Non-current: | | | | |
| U.S. Treasuries | 125,447 | 5 | (70) | 125,382 |
| | $ 453,473 | $ 50 | $ (107) | $ 453,416 |

Marketable securities at December 31, 2013 consist of the following (in thousands):

| | Amortized Cost | Unrealized Gains | Unrealized Losses | Fair Value |
|---|---|---|---|---|
| Current: | | | | |
| Certificates of deposit | $ 6,920 | $ — | $ (5) | $ 6,915 |
| U.S. Treasuries | 88,287 | 8 | (1) | 88,294 |
| Non-current: | | | | |
| U.S. Treasuries | 27,113 | 12 | — | 27,125 |
| | $ 122,320 | $ 20 | $ (6) | $ 122,334 |

At December 31, 2014 and 2013, the Company held both current and non-current investments. Investments classified as current have maturities of less than one year. Investments classified as non-current are those that

(i) have maturities of one to two years and (ii) management does not intend to liquidate within the next twelve months, although these funds are available for use and therefore classified as available-for-sale.

At December 31, 2014 and 2013, the Company held 92 and 33 debt securities, respectively, that were in an unrealized loss position for less than one year. The aggregate fair value of debt securities in an unrealized loss position at December 31, 2014 and 2013 was $236.9 million and $31.7 million, respectively. There were no individual securities that were in a significant unrealized loss position or that had been in an unrealized loss position for greater than one year as of December 31, 2014 and 2013. The Company evaluated its securities for other-than-temporary impairment and considered the decline in market value for the securities to be primarily attributable to current economic and market conditions. It is not more likely than not that the Company will be required to sell the securities, and the Company does not intend to do so prior to the recovery of the amortized cost basis. Based on this analysis, these marketable securities were not considered to be other-than-temporarily impaired as of December 31, 2014 and 2013.

***Concentrations of Credit Risk***

Financial instruments which potentially subject the Company to credit risk consist primarily of cash, cash equivalents and marketable securities. The Company holds these investments in highly rated financial institutions, and, by policy, limits the amounts of credit exposure to any one financial institution. These amounts at times may exceed federally insured limits. The Company has not experienced any credit losses in such accounts and does not believe it is exposed to any significant credit risk on these funds. The Company has no off-balance sheet concentrations of credit risk, such as foreign currency exchange contracts, option contracts or other hedging arrangements.

The Company is also subject to credit risk from its collaboration receivable. The Company evaluates the creditworthiness of its collaborator and has determined it is credit worthy. To date the Company has not experienced any losses with respect to its collaboration receivable.

***Fair Value Measurements***

The Company records cash equivalents and marketable securities at fair value. ASC Topic 820, *Fair Value Measurements and Disclosures*, establishes a fair value hierarchy for those instruments measured at fair value that distinguishes between assumptions based on market data (observable inputs) and the Company's own assumptions (unobservable inputs). The hierarchy consists of three levels:

*Level 1* – Unadjusted quoted prices in active markets for identical assets or liabilities.

*Level 2* – Quoted prices for similar assets and liabilities in active markets, quoted prices in markets that are not active, or inputs which are observable, either directly or indirectly, for substantially the full term of the asset or liability.

*Level 3* – Unobservable inputs that reflect the Company's own assumptions about the assumptions market participants would use in pricing the asset or liability in which there is little, if any, market activity for the asset or liability at the measurement date.

The following table summarizes the cash equivalents and marketable securities measured at fair value on a recurring basis as of December 31, 2014 (in thousands):

| | Level 1 | Level 2 | Level 3 | Total |
|---|---|---|---|---|
| Cash equivalents | $ 11,410 | $ 960 | $ — | $ 12,370 |
| Marketable securities: | | | | |
| Certificates of deposit | — | 13,155 | — | 13,155 |
| U.S. Treasuries | 440,261 | — | — | 440,261 |
| | $ 451,671 | $ 14,115 | $ — | $ 465,786 |

The following table summarizes the cash equivalents and marketable securities measured at fair value on a recurring basis as of December 31, 2013 (in thousands):

| | Level 1 | Level 2 | Level 3 | Total |
|---|---|---|---|---|
| Cash equivalents | $ 68,792 | $ — | $ — | $ 68,792 |
| Marketable securities: | | | | |
| Certificates of deposit | — | 6,915 | — | 6,915 |
| U.S. Treasuries | 115,419 | — | — | 115,419 |
| | $ 184,211 | $ 6,915 | $ — | $ 191,126 |

Cash equivalents and marketable securities have been initially valued at the transaction price and subsequently valued, at the end of each reporting period, utilizing third party pricing services or other market observable data. The pricing services utilize industry standard valuation models, including both income and market based approaches and observable market inputs to determine value. The Company validates the prices provided by its third party pricing services by reviewing their pricing methods and obtaining market values from other pricing sources. After completing its validation procedures, the Company did not adjust or override any fair value measurements provided by the pricing services as of December 31, 2014 or 2013.

The carrying amounts reflected in the consolidated balance sheets for cash, restricted cash, collaboration receivable – related party, prepaid expenses and other current assets, other assets, accounts payable, and accrued expenses approximate their fair values at December 31, 2014 and 2013, due to their short-term nature.

There have been no changes to the valuation methods during the years ended December 31, 2014 and 2013. The Company evaluates transfers between levels at the end of each reporting period. There were no transfers of assets or liabilities between Level 1 and Level 2 during the years ended December 31, 2014 and 2013. The Company had no financial assets or liabilities that were classified as Level 3 at any point during the years ended December 31, 2014 and 2013.

***Collaboration and Other Receivables***

Collaboration receivables as of December 31, 2014 represent amounts due from Celgene for cost reimbursements of certain on-going phase 1 studies under the Celgene Agreement. As of December 31, 2013, collaboration receivables represented an unbilled collaboration receivable for revenues recognized related to Celgene's election to extend the term of the initial discovery period from four to five years. Other receivables represent amounts due from the Company's landlord for reimbursement of tenant improvements under the Company's lease agreement.

The Company estimates an allowance for doubtful accounts based on credit worthiness, historical payment patterns, aging of accounts receivable balances, and general economic conditions. As of December 31, 2014 and 2013, the Company had no allowance for doubtful accounts.

***Property and Equipment***

Property and equipment consist of laboratory equipment, computer equipment and software, leasehold improvements, furniture and fixtures, and office equipment. Property and equipment is stated at cost, and depreciated using the straight-line method over the estimated useful lives of the respective assets:

| | |
|---|---|
| Laboratory equipment | 5 years |
| Computer equipment and software | 3 years |
| Leasehold improvements | Shorter of asset's useful life or remaining term of lease |
| Furniture and fixtures | 5 years |
| Office equipment | 5 years |

Costs of major additions and betterments are capitalized; maintenance and repairs, which do not improve or extend the life of the respective assets, are charged to expense as incurred. Upon retirement or sale, the cost of the disposed asset and the related accumulated depreciation are removed from the accounts and the resulting gain or loss is recognized.

***Impairment of Long-Lived Assets***

The Company periodically evaluates its long-lived assets for potential impairment in accordance with ASC Topic 360, *Property, Plant and Equipment*. Potential impairment is assessed when there is evidence that events or changes in circumstances indicate that the carrying amount of an asset may not be recovered. Recoverability of these assets is assessed based on undiscounted expected future cash flows from the assets, considering a number of factors, including past operating results, budgets and economic projections, market trends and product development cycles. If impairments are identified, assets are written down to their estimated fair value. The Company has not recognized any impairment charges through December 31, 2014.

***Segment and Geographic Information***

Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision maker, or decision making group, in making decisions on how to allocate resources and assess performance. The Company's chief operating decision maker is the chief executive officer. The Company and the chief decision maker view the Company's operations and manage its business as one operating segment. The Company operates in only one geographic segment.

***Net Loss per Share Applicable to Common Stockholders***

Basic net loss per share applicable to common stockholders is calculated by dividing net loss applicable to common stockholders by the weighted average shares outstanding during the period, without consideration for common stock equivalents. Net loss applicable to common stockholders is calculated by adjusting the net loss of the Company for cumulative preferred stock dividends. Diluted net loss per share applicable to common stockholders is calculated by adjusting weighted average shares outstanding for the dilutive effect of common stock equivalents outstanding for the period, determined using the treasury-stock method. For purposes of the dilutive net loss per share applicable to common stockholders calculation, preferred stock, stock options, and unvested restricted stock are considered to be common stock equivalents but are excluded from the calculation of diluted net loss per share applicable to common stockholders as their effect would be anti-dilutive; therefore, basic and diluted net loss per share applicable to common stockholders were the same for all periods presented. The following common stock equivalents were excluded from the calculation of diluted net loss per share applicable to common stockholders for the periods indicated because including them would have had an anti-dilutive effect:

| | Years ended December 31, | | |
|---|---|---|---|
| | **2014** | **2013** | **2012** |
| Convertible preferred stock | - | - | 19,731,564 |
| Stock options | 3,805,420 | 3,846,168 | 3,145,544 |
| Unvested restricted stock | 8,522 | 23,295 | 160,053 |
| Employee stock purchase plan shares | 7,159 | - | - |
| | 3,821,101 | 3,869,463 | 23,037,161 |

***Recent Accounting Pronouncements***

In August 2014, the FASB issued ASU No. 2014-15, *Presentation of Financial Statements—Going Concern (Subtopic 205-40)*. The ASU requires all entities to evaluate for the existence of conditions or events that raise substantial doubt about the entity's ability to continue as a going concern within one year after the issuance date of the financial statements. The accounting standard is effective for interim and annual periods ending after December 15, 2016, and will not have a material impact on the consolidated financial statements, but may impact the Company's footnote disclosures.

In June 2014, the FASB issued ASU No. 2014-12, *Compensation—Stock Compensation (Topic 718)*. The ASU clarifies how entities should treat performance targets that can be achieved after the requisite service period of a share-based payment award. The accounting standard is effective for interim and annual periods beginning after December 15, 2015 and is not expected to have a material impact on the consolidated financial statements.

In May 2014, the FASB issued ASU No. 2014-09, *Revenue from Contracts with Customers (Topic 606)*. The ASU provides for a single comprehensive model for use in accounting for revenue arising from contracts with customers and supersedes most current revenue recognition guidance. The accounting standard is effective for interim and annual periods beginning after December 15, 2016 with no early adoption permitted. The Company is required to adopt the amendments in the ASU using one of two acceptable methods. The Company is currently in the process of determining which adoption method it will apply and evaluating the impact of the guidance on its consolidated financial statements.

Other accounting standards that have been issued by the FASB or other standards-setting bodies that do not require adoption until a future date are not expected to have a material impact on the Company's financial statements upon adoption.

***Subsequent Events***

The Company considered events or transactions occurring after the balance sheet date but prior to the issuance of the consolidated financial statements are available to be issued for potential recognition or disclosure in its consolidated financial statements. All significant subsequent events have been properly disclosed in the consolidated financial statements.

**3. Collaboration Agreement**

In April 2010, the Company entered into a collaboration agreement focused on cancer metabolism with Celgene, a related party through ownership of the Company's common stock. The agreement was amended in October 2011 and in July 2014, as described below. The goal of the collaboration is to discover, develop and commercialize disease-altering therapies in oncology based on the Company's cancer metabolism research platform. The Company is leading discovery, preclinical and early clinical development for all cancer metabolism programs under the collaboration. The discovery phase of the amended collaboration was to expire in April 2014, subject to Celgene's option to extend the discovery phase for up to an additional two years with additional funding to the Company. In December 2013, Celgene elected to extend the term of the initial discovery phase from four years to five years, to April 2015, in exchange for the payment of a $20.0 million extension fee which was received in May 2014. In December 2014, Celgene elected to exercise its final option to extend the term of the initial discovery phase one additional year, to April 2016, in exchange for the payment of a $20.0 million extension fee which is expected to be received in the second quarter of 2015.

Pursuant to the collaboration agreement and subsequent amendments, the Company was responsible for nominating development candidates, of which two required confirmation by the Joint Research Committee

("JRC") during the discovery phase. During the year ended December 31, 2012 the Company nominated its first development candidate and during the year ended December 31, 2013 the Company nominated its second development candidate, both of which have been confirmed by the JRC pursuant to the agreement. For each development candidate, Celgene elected to progress such development candidate into preclinical development requiring the Company to conduct studies to meet the requirements for filing an Investigational New Drug application ("IND"), or IND-enabling studies. Subsequently, the Company was required to file an IND for each development candidate and, upon the FDA's acceptance of the INDs, Celgene requested that the Company conduct an initial phase 1 study.

Celgene may elect to convert each discovery program for which the Company has nominated a development candidate into a co-commercialized licensed program, the attributes of which are described below. The Company has 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 the Company will retain the United States rights, other attributes of which are further described below. In June 2014, Celgene exercised its option to an exclusive global license for the development and commercialization of the Company's isocitrate dehydrogenase 2 ("IDH2") program, AG-221. The Company elected to retain U.S. rights to its isocitrate dehydrogenase 1 ("IDH1") program, AG-120, in January 2014. In January 2015, Celgene agreed to exercise its rights to this program subject to receipt of any required regulatory approvals upon which the program will become a split licensed program. In addition, Celgene may license certain discovery programs that the Company does not nominate or the JRC does not confirm as a development candidate and for which Celgene will lead and fund global development and commercialization.

The Company will retain the rights to development candidates and certain other compounds 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 the Company 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.

The agreement provides for three types of licensed programs as discussed above:

*Co-Commercialized Licensed Programs:* Celgene will lead and, following either IND acceptance by the FDA or, if Celgene requests the Company to conduct the initial phase 1 study upon completion of such phase 1 study, will fund global development and commercialization. The Company has the right to participate in a portion of sales activities in the United States for products from co-commercialized programs in accordance with the applicable commercialization plan. The Company will be eligible to receive milestone payments and royalties arising from the licensed program.

*Split Licensed Programs:* Celgene will lead development and commercialization outside the United States and the Company will lead development and commercialization in the United States. The Company 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 the Company will be responsible for development and commercialization costs specific to the United States. The Company will retain profits generated in the United States and will also be eligible to receive milestone payments and royalties arising from net sales outside the United States. The Company will be obligated to pay Celgene royalties arising from net sales in the United States.

*Buy-In Programs:* If a party elects to independently undertake a discovery program, with respect to a particular target under the agreement, the party that is conducting the independent program that becomes 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 products from such buy-in program. The commercializing party will be obligated to pay the buy-in party specified royalties on worldwide net sales.

The term of the agreement will continue, unless earlier terminated by either party, until the expiration of the last-to-expire of all royalty terms with respect to all royalty-bearing products. Celgene may terminate the agreement for convenience in its entirety or with respect to one or more programs upon ninety days written notice to the Company. Either the Company 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 only terminate the agreement with respect to such program. Either the Company or Celgene may terminate the agreement in the event of specified insolvency events involving the other party.

Under the terms of the agreement, the Company received an upfront payment of approximately $121.2 million. In addition, Celgene purchased 5,190,551 shares of Series B convertible preferred stock ("Series B Preferred Stock") at a price of $1.70 per share, resulting in net proceeds to the Company of approximately $8.8 million. The Company determined the price paid by Celgene for the Series B Preferred Stock represented a premium over the fair value of the Company's Series B Preferred Stock as determined by the implied value of the Series B Preferred Stock pursuant to a contemporaneous valuation analysis that allocated the equity value of the Company to the various classes of its then-outstanding securities. The Company accounted for the $3.1 million premium as additional consideration under the agreement and the Series B Preferred Stock was recorded at its fair value of $5.7 million. In connection with the 1-for-2.75 reverse stock split of the Company's common stock, the shares of Series B Preferred Stock converted into 1,887,473 shares of common stock upon the closing of the Initial Public Offering in July 2013.

In October 2011, the agreement was amended to extend the term of the initial discovery period from three to four years, to April 2014. The amendment was not deemed to be a material modification to the arrangement, pursuant to ASU No. 2009-13, since there were no changes in the deliverables or the total arrangement consideration, as the provisions of the original agreement provided Celgene with the option to extend the research period for the same consideration. Celgene made a payment to the Company of $20.0 million pursuant to the amendment. The payment was combined with the unamortized upfront payment and premium and was recognized as revenue on a straight-line basis over the estimated performance period prior to the July 2014 amendment described below.

In December 2013, Celgene elected to extend the term of the initial discovery period from four to five years, to April 2015. As a result of the extension, the Company received a $20.0 million extension payment from Celgene in May 2014. The payment was combined with the unamortized upfront payment, premium, and prior extension payment and was being recognized as revenue on a straight-line basis over the estimated performance period prior to the July 2014 amendment described below.

In July 2014, the Company amended the collaboration agreement to allow for more flexibility in the design and conduct of phase 1 clinical trials and additional nonclinical and/or clinical activities that the Company agrees to perform at Celgene's request. The amendment further modifies the mechanism and timing for payments to be made with respect to such development activities. The amendment was determined to be a material modification pursuant to ASU No. 2009-13, due to a change in the total potential consideration that was more than insignificant and changes to certain of the deliverables in the arrangement. The amendment impacts the co-commercialized and split licensed programs as follows:

- Co-commercialized licensed programs: The amendment modifies the timing and nature of the consideration for the development efforts related to an initial phase 1 study from a milestone due at the

completion of the study to payments due upon the earlier of the determination of the maximum tolerated dose or Celgene's election to license the program.

- Split licensed programs: The amendment allows for the Company to receive reimbursement for costs and expenses it incurs for any disease-specific expansion cohort within a phase 1 clinical trial design, provided that the disease-specific expansion cohort supports the initiation of a subsequent pivotal clinical trial. The milestone reimbursement is the lesser of fifty percent of the costs incurred by the Company for disease specific cohorts and $10 million and is payable upon the first patient dosed within the corresponding pivotal trial.

Prior to the amendment, the Company concluded that none of the identified deliverables had stand-alone value and, therefore, accounted for the deliverables as a single unit of accounting. The Company further concluded it was unable to estimate the fair value of the undelivered items within the agreement. Consideration received was recognized on a straight-line basis through the period over which the Company expected to fulfill its performance obligations (the performance period), which was initially determined to be 6 years.

Upon concluding the arrangement had been materially modified in July 2014, the Company identified the remaining deliverables under the arrangement and determined its best estimate of selling price for the undelivered elements as of the modification date. The Company then allocated the total arrangement consideration, which included the remaining deferred revenue balance at the modification date and other consideration that was deemed to be determinable at the modification date, to each unit of accounting based on its best estimate of selling price. The difference between the total consideration and the best estimate of selling price of the undelivered items was recorded as revenue at the modification date. The undelivered items, which are each considered by the Company to have stand-alone value and therefore are separate units of accounting, the related best estimate of selling price, and the method of recognizing the allocated consideration, for each unit of accounting are as follows:

- License for the split licensed program – AG-120: The Company developed the best estimate of selling price of the license by probability weighting multiple cash flow scenarios using the income approach. Management estimates within the models include the expected, probability-weighted net profits from estimated future sales, an estimated royalty rate using comparable industry royalty agreements, an estimate of the direct costs incurred to generate future cash flows, a discount rate, an estimated contributory asset charge rate to reflect the cost associated with the use of other assets to generate the cash flow, an estimated income tax rate and other business forecast factors. There are significant judgments and estimates inherent in the determination of the best estimate of selling price of this unit of accounting. These judgments and estimates include assumptions regarding future operating performance, the timelines of the clinical trials and regulatory approvals and the estimated patient populations. Should different reasonable assumptions be utilized, the best estimate of selling price and the associated revenues recognized would be different. Based on the analysis using management's best estimate, the Company allocated $21.2 million to the license and will recognize revenue upon Celgene's election to exercise its option to the split licensed program – AG-120. The Company will immediately recognize the non-contingent allocated consideration on the exercise date. On January 12, 2015, Celgene agreed to exercise its option to obtain an exclusive license outside the United States for AG-120, subject to receipt of any required regulatory approvals including any applicable clearance under the Hart-Scott-Rodino Act.
- Development services for five separate on-going phase 1 studies (each of which is a separate unit of accounting): The Company developed the best estimate of selling price of the on-going phase 1 study development services of $50.8 million for all five studies using management's best estimate of the cost of obtaining these services from a third-party provider, as well as internal full time equivalent costs to

support the development services. The estimated costs were determined to represent management's best estimate of the price these services could be sold for separately. The amount allocated to these units of accounting is being recognized as revenue on a proportional performance basis as services are provided. The Company expects the performance period for these units of accounting to be delivered through the second quarter of 2016.

- On-going research and development: The Company developed the best estimate of selling price of the research and development services of $13.6 million using management's best estimate of the cost of obtaining these services from a third-party provider. The amount allocated to this unit of accounting is being recognized as revenue ratably over the performance period. The performance period has been determined to be through April 2015.
- Committee participation: The Company developed the best estimate of selling price of the committee participation services of $0.2 million using management's best estimate of the anticipated participation hours multiplied by a market rate for comparable participants. The amount allocated to this unit of accounting is being recognized as revenue ratably over the performance period. The performance period has been determined to be through April 2015.

The total estimated arrangement consideration, as well as the expected timing of revenue recognition, is adjusted based on changes in estimated arrangement consideration as a result of changes in estimate for certain on-going phase 1 studies. The allocable consideration will increase as the Company performs certain services for which it is eligible to receive reimbursement. These amounts will be recognized on a cumulative catch-up basis for any in-process units of accounting or immediately for any fully delivered units of accounting. For the period January 1, 2014 through the amendment date, the Company recognized a total of $42.7 million in revenues under the previous accounting guidance and upon the material modification. The Company recognized total revenue of $65.4 million, $25.5 million, and $25.1 million in connection with the Celgene collaboration during the years ended December 31, 2014, 2013, and 2012, respectively.

In December 2014, Celgene elected to extend the term of the initial discovery period from five to six years, to April 2016. As a result of the extension, the Company is entitled to receive a $20.0 million extension payment from Celgene. The Company evaluated this substantive option upon the material modification and concluded that upon exercise it is obligated provide its committee participation and research and development services for a period of one year from April 2015 through April 2016. Revenue will be recognized ratably over the performance period of April 2015 to April 2016 as the services are performed. The Company did not recognize any revenue related to this substantive option during the year ended December 31, 2014.

Under the arrangement, the Company is eligible to receive up to $120.0 million in potential milestone payments payable for each program selected by Celgene. The potential milestone payments for each such 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. The Company is also eligible to receive additional milestone payments specific to co-commercialized licensed programs and split licensed programs. In addition, the Company is eligible to receive a substantive milestone payment of $22.5 million upon achievement of an early clinical development milestone event for certain co-commercialized licensed programs. In connection with the first split licensed program under the collaboration, the Company's IDH1 program, AG-120, the Company is eligible to receive an additional one-time payment of $25.0 million upon the dosing of the last patient in a Company-sponsored phase 2 clinical trial.

In addition to the milestone payments described above, for each co-commercialized licensed program, the Company 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 the Company 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. Through December 31, 2014, the Company had earned $26.6 million in cost reimbursements which includes the initial milestone payment. As of December 31, 2014, the Company has recorded a collaboration receivable of $6.5 million related to reimbursable development costs for AG-221.

In addition to the milestone payments described above, for each split licensed program, the Company is eligible for reimbursement of the costs of disease-specific expansion cohort(s) that support 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 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.

The Company has concluded that certain of the clinical development and regulatory milestones that may be received under the Celgene agreement, if the Company is involved in future product development and commercialization, are substantive. Factors considered in the evaluation of the milestones included the degree of risk associated with performance of the milestone, the level of effort and investment required, whether the milestone consideration was reasonable relative to the deliverables and whether the milestone was earned at least in part based on the Company's performance. Revenues from substantive milestones, if they are nonrefundable, are recognized as revenue upon successful accomplishment of the milestones. Clinical and regulatory milestones are deemed non-substantive if they are based solely on the collaborator's performance. Non-substantive milestones will be recognized when achieved to the extent the Company has no remaining performance obligations under the arrangement. Milestone payments earned upon achievement of commercial milestone events will be recognized when earned.

The Company may also receive royalties at tiered, low- to mid-teen percentage rates on net sales and has the option to participate in the development and commercialization of certain products in the United States. The royalty payments are recognized as revenue in the period in which they are earned. No other milestone or royalty payments under the agreement have been earned.

**4. Property and Equipment**

Property and equipment consists of the following (in thousands):

| | December 31, | |
|---|---|---|
| | 2014 | 2013 |
| Laboratory equipment | $ 6,885 | $ 5,754 |
| Computer equipment and software | 1,458 | 1,056 |
| Leasehold improvements | 97 | 97 |
| Furniture and fixtures | 345 | 342 |
| Office equipment | 218 | 218 |
| Construction in progress | 2,941 | 482 |
| Total property and equipment | 11,944 | 7,949 |
| Less accumulated depreciation | (5,558) | (4,191) |
| Total property and equipment, net | $ 6,386 | $ 3,758 |

Depreciation expense for the years ended December 31, 2014, 2013 and 2012 was $1.4 million, $1.4 million and $1.2 million, respectively.

**5. Accrued Expenses and Other Current Liabilities**

Accrued expenses and other current liabilities consist of the following (in thousands):

| | December 31, | |
|---|---|---|
| | 2014 | 2013 |
| Accrued compensation | $ 5,689 | $ 3,642 |
| Accrued contracted research and development costs | 7,340 | 2,484 |
| Accrued professional fees | 549 | 320 |
| Accrued other | 442 | 140 |
| Total | $ 14,020 | $ 6,586 |

**6. Commitments and Contingencies**

***Operating Lease***

On September 15, 2014, the Company entered into an operating lease agreement (the "Lease") for approximately 74,500 square feet of office and laboratory space located at 88 Sidney Street, Cambridge, Massachusetts. Concurrently, the Company also entered into an agreement to terminate its existing lease under which the Company currently leases approximately 38,500 square feet of office and laboratory space located at 38 Sidney Street, Cambridge, Massachusetts. On November 21, 2014, the Company entered into a first amendment to the Lease (the "Lease Amendment") to expand the rentable square footage of the leased space at 88 Sidney Street to approximately 113,200 square feet.

The date on which the Company will become responsible for paying rent under the Lease, as amended by the Lease Amendment (the "Commencement Date") will be the earlier of May 15, 2015 or the date upon which the Company first begins conducting business at the new location. The Company's existing lease at 38 Sidney Street will terminate thirty days after the Commencement Date. The initial lease term will be for a period of seven years from the Commencement Date. At the end of the lease term, the Company has the option to extend the Lease for two consecutive terms of five years at the fair market rent at the time of the extension. The lease agreement includes rent escalation clauses and a tenant improvement allowance of $16.5 million. The Company gained physical access to the leased space in September 2014 and began to record rent expense on a straight-line basis over the effective term of the Lease. The Company gained physical access to the expanded space in November 2014. The Company provided a standby letter of credit of $2.2 million as security for its obligations under the Lease in December 2014. The Company was not required to maintain any cash collateral for the standby letter of credit due to its good standing with the lender.

At December 31, 2014, the Company recorded approximately $2.3 million in tenant improvement allowance to be received from the Company's landlord and is recorded as construction in progress within property and equipment, net, and in deferred rent and deferred rent, net of current portion, in the consolidated balance sheets. The deferred rent will be recorded as a reduction in rent expense ratably over the lease term.

Future annual minimum lease payments due under non-cancellable operating leases at December 31 of each year are as follows (in thousands):

| | |
|---|---|
| 2015 | $ 4,990 |
| 2016 | 6,685 |
| 2017 | 6,842 |
| 2018 | 7,004 |
| 2019 | 7,169 |
| Thereafter | 17,691 |
| | $ 50,381 |

Rent expense was $3.7 million, $2.2 million and $2.2 million for the years ended December 31, 2014, 2013 and 2012, respectively. The operating leases require the Company to share in prorated operating expenses and property taxes based upon actual amounts incurred; those amounts are not fixed for future periods and, therefore, are not included in the future commitments listed above.

***Lead Program License Agreement***

In August 2012, the Company entered into a license agreement pursuant to which the licensor granted the Company a worldwide exclusive license to certain intellectual property rights for the development of diagnostic products to detect the metabolism of certain cancers. The Company is obligated to pay the licensor up to $100,000 in milestone payments, contingent upon the issuance of certain patents. For each product developed under the agreement the Company has the right to elect to develop and commercialize the product or to grant the licensor an exclusive license to develop and commercialize the product. Under the agreement, the applicable party will pay to the other party a royalty based on worldwide net sales of products. As of December 31, 2014, the Company accrued $50,000 related to milestones achieved; however, there have been no sales of products licensed.

The term of the agreement will continue, unless earlier terminated by either party, until the expiration of the last-to-expire issued patent. Either party may terminate the agreement in the event of the failure of the other party to make required payments under the agreement or an uncured material breach by the other party. In addition, the licensor may terminate the agreement if the Company becomes insolvent or challenges certain licensed patent rights.

***Other Program License Agreements***

The Company has entered into various cancelable license agreements for certain technology. None of the Company's lead product candidates utilize technology covered by these licenses. In consideration for the licensed rights the Company made up-front payments totaling $470,000 and issued a total of 162,545 shares of common stock to certain licensors. During the year ended December 31, 2014, the Company paid annual maintenance payments totaling $42,000 to certain of the licensors, which are recorded as research and development expense. The Company has the option to renew these licenses on an annual basis in exchange for payments approximating $45,000 for 2015. The Company could be required to make patent-related, clinical development, regulatory and sales-based milestones of up to $0.1 million, $1.6 million, $5.4 million and $4.2 million, respectively, to the licensors. The license agreements also require the Company to remit royalties in amounts ranging from 0.5% to 2.5% based on net sales of products utilizing the licensed technology. The Company is also required to make payments in amounts ranging from 7.0% to 25.0% for non-royalty income received from any sublicense of the rights granted to the Company under the agreements. Total license expense

incurred under the license agreements amounted to approximately $83,000, $72,000 and $30,000 during the years ended December 31, 2014, 2013 and 2012, respectively. The Company incurred $50,000 and $25,000 in patent-based milestones expenses in 2014 and 2013, respectively. The Company did not pay any milestones in 2012 and the Company has paid no royalties to date.

***Milestone Payment Agreements***

The Company entered into an agreement with a service provider to receive discounted upfront labor costs for a defined program in consideration of a milestone payment in five years from the Effective Date, as defined in the agreement. The milestone is dependent on the Company declaring a development candidate within the five-year contract term and is dependent on the origins of the development candidate. If the development candidate is derived from a new chemical class created by the service provider, the milestone will be two times the discounted upfront labor costs. If the development candidate is not derived from a new chemical class created by the service provider, the milestone will be equal to the discount on services provided to date. No milestone payment is due if no development candidate is declared within the five year period. In addition, should no development candidate be declared within three years and the Company remains active with the program, the service provider may, at its discretion, elect to request reimbursement of the discount on services provided to date and forgo the milestone payment. The election must be provided in writing within thirty days of the end of the three-year period. The accumulated discounted labor costs through December 31, 2014 are approximately $1.0 million. The Company has not accrued for the accumulated discount under the reimbursement option as the Company is currently unable to determine the probability of a development candidate being declared within a three-year period.

The Company entered into an agreement to utilize certain technologies and services in exchange for agreed upon rates over a period of time. The Company made an up-front payment of approximately $0.1 million upon execution of the agreement. The agreement includes milestone payments related to regulatory and preclinical events. The Company paid $0.3 million in regulatory milestones in the year ended December 31, 2014 and paid $0.2 million in preclinical milestones and $0.2 million in regulatory milestones in the year ended December 31, 2013. The Company did not pay any milestones in the year ended December 31, 2012. Total expenses incurred under this agreement amounted to approximately $0.3 and $0.4 million in the years ended December 31, 2014 and 2013, respectively. There were no expenses incurred under this agreement in the year ended December 31, 2012. As of December 31, 2013, the Company no longer had any milestone payment obligation remaining under this agreement.

***Other Agreement***

On November 10, 2009, the Company entered into a research funding agreement whereby the Company received upfront grant consideration to be utilized in the development and testing of brain cancer therapies in exchange for three separate $178,538 milestone payments. The milestones can be earned over a ten-year period from the agreement date and are dependent on the Company successfully commercializing a brain cancer therapy product. The Company will make separate milestone payments when it accumulates net profits of $5.0 million, $50.0 million and $250.0 million, respectively, from sales of the product. As of December 31, 2014, the Company has not commercialized a brain cancer therapy product.

**Legal Contingencies**

From time to time, the Company may be involved in disputes and legal proceedings in the ordinary course of its business. These proceedings may include allegations of infringement of intellectual property, employment or other matters. The Company does not have any ongoing legal proceedings that, based on management estimates, could have a material effect on the Company’s consolidated financial statements.

Agios Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (continued)

**7. Convertible Preferred Stock**

In 2008 and 2009, the Company sold a total of 33,188,889 shares of Series A convertible preferred stock to investors at $1.00 per share, resulting in aggregate proceeds of $33.1 million, including the conversion of the principal and interest on $2.0 million of convertible notes.

In April 2010, the Company executed a strategic collaboration agreement with Celgene Corporation (Note 3). In connection with the Celgene Agreement, the Company sold 5,190,551 shares of Series B convertible preferred stock (Series B Preferred Stock) to Celgene at $1.70 per share, resulting in aggregate proceeds of $8.8 million. The Company determined the fair value per share of the Series B Preferred Stock on the date of issuance to be $1.11 and has considered the premium paid over the fair value of the Series B Preferred Stock to be additional consideration under the Celgene Agreement. Refer to Note 3 for further discussion of the treatment of the implied premium on the Series B Preferred Stock.

In November 2011, the Company completed a Series C convertible preferred stock financing, pursuant to which the Company sold 15,882,389 shares of Series C convertible preferred stock to investors at $4.91 per share, resulting in aggregate proceeds of $78.0 million. The shares of Series C convertible preferred stock included 7,395,829 shares of Series C-1 convertible preferred stock (the C-1 Preferred Stock) and 8,486,560 shares of Series C-2 convertible preferred stock (the C-2 Preferred Stock) (collectively, the Series C Preferred Stock).

The Company assessed the Series A, B and C Preferred Stock (collectively, the "Preferred Stock") for any embedded derivatives that would require bifurcation from the Preferred Stock and receive separate accounting treatment. No embedded derivatives were identified that would require bifurcation.

In connection with the closing of the IPO, all of the Company's outstanding convertible Preferred Stock automatically converted to common stock, resulting in an additional 19,731,564 shares of common stock of the Company becoming outstanding. Further, under the terms of the certificate of incorporation, the Board of Directors is authorized to direct the Company to issue shares of Preferred Stock in one or more series without stockholder approval. The Board of Directors has the discretion to determine the rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences, of each series of Preferred Stock. As of December 31, 2014, there are no shares of Preferred Stock outstanding.

Prior to the IPO, the holders of Series A, Series B, and Series C Preferred Stock were entitled to receive cumulative dividends at the rate of $0.06, $0.10, and $0.294666 per share per annum, respectively, in preference to any dividends on common stock, when, as, and if declared by the Board of Directors. These dividends were cumulative and accrued whether or not declared. As of December 31, 2012, dividends accrued but unpaid were $7.8 million for Series A Preferred Stock, $1.4 million for Series B Preferred Stock, and $5.3 million for Series C Preferred Stock. Immediately prior to the IPO, dividends accrued but unpaid were $8.9 million for Series A Preferred Stock, $1.7 million for Series B Preferred Stock, and $8.0 million for Series C Preferred Stock.

**8. Common Stock**

In connection with the IPO, the Company's Board of Directors and stockholders approved a 1-for-2.75 reverse stock split of the Company's common stock. The reverse stock split became effective on July 11, 2013. All share and per share amounts in the consolidated financial statements have been retroactively adjusted for all periods presented to give effect to this reverse stock split, including reclassifying an amount equal to the reduction in par value of common stock to additional paid-in capital. The Company's common stock has the following characteristics:

***Voting***

The holders of shares of common stock are entitled to one vote for each share of common stock held at all meetings of stockholders and written actions in lieu of meetings.

***Dividends***

The holders of shares of common stock are entitled to receive dividends, if and when declared by the board of directors and are subject to any preferential dividend or other right of any then outstanding preferred stock. No dividends have been declared or paid since the Company's inception.

***Liquidation***

The holders of shares of common stock are entitled to share ratably in the Company's assets available for distribution to stockholders, in the event of any voluntary or involuntary liquidation, subject to any preferential or other rights of any then outstanding preferred stock.

**9. Share-Based Payments**

***Stock Incentive Plans***

Prior to the IPO, the Company maintained the 2007 Stock Incentive Plan (the "2007 Plan") for employees, directors, consultants, and advisors to the Company. The 2007 Plan provided for the grant of incentive and non-qualified stock options and restricted stock grants as determined by the Board of Directors. Under the 2007 Plan, the Company reserved 5,079,462 shares of common stock and, at December 31, 2014 and December 31, 2013, the Company had no shares available for future issuance.

In June 2013, the Company's Board of Directors adopted, and in July 2013, the Company's stockholders approved, the 2013 Stock Incentive Plan (the "2013 Plan"). The 2013 Plan became effective upon the closing of the IPO and provides for the grant of incentive stock options, non-qualified stock options, stock appreciation rights, restricted stock awards, restricted stock units and other stock-based awards. The Company will grant no further stock options or other awards under the 2007 Plan. Any options or awards outstanding under the 2007 Plan at the time of adoption of the 2013 Plan remain outstanding and effective. As of December 31, 2014, the total number of shares reserved under all equity plans is 4,445,395, and the Company had 639,975 shares available for future issuance under such plans. The 2013 Plan provides for an annual increase, to be added on the first day of each fiscal year, beginning with the fiscal year ending December 31, 2014 and continuing until the expiration of the 2013 Plan, equal to the lesser of (i) 2,000,000 shares of common stock, (ii) 4% of the outstanding shares of common stock on such date or (iii) an amount determined by the Company's Board of Directors. On January 1, 2015, the annual increase for the 2013 Plan resulted in an additional 1,484,020 shares authorized for issuance.

Agios Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (continued)

During the year ended December 31, 2014 the Company did not grant any stock options to consultants and advisors of the Company. During the year ended December 31, 2013, consultants and advisors were granted 27,272 stock options. These awards are included within the following table which summarizes the stock option activity of all stock incentive plans for the year ended December 31, 2014.

| | Number of Stock Options | Weighted-Average Exercise Price | Weighted-Average Remaining Contractual Term (in years) | Aggregate Intrinsic Value (in thousands) |
|---|---|---|---|---|
| Outstanding at December 31, 2013 | 3,846,168 | $ 4.14 | 7.43 | $ 76,189 |
| Granted | 1,339,483 | 39.49 | | |
| Exercised | (1,298,775) | 1.79 | | |
| Forfeited/Expired | (81,456) | 13.22 | | |
| Outstanding at December 31, 2014 | 3,805,420 | $ 17.19 | 7.58 | $ 360,935 |
| Exercisable at December 31, 2014 | 1,577,101 | $ 2.58 | 5.82 | $ 172,636 |
| Vested and expected to vest at December 31, 2014 | 3,516,545 | $ 16.98 | 7.50 | $ 334,292 |

The weighted-average grant date fair value of options granted was $27.26, $9.96 and $2.09 during the years ended December 31, 2014, 2013 and 2012, respectively. The total intrinsic value of options exercised was $60.4 million, $4.2 million and $0.8 million during the years ended December 31, 2014, 2013 and 2012, respectively.

At December 31, 2014, the total unrecognized compensation expense related to unvested stock option awards, including estimated forfeitures, was $32.5 million, which the Company expects to recognize over a weighted-average period of approximately 3.1 years. The Company also has unrecognized stock-based compensation expense of $1.1 million related to stock options with performance-based vesting criteria that are not considered probable of achievement as of December 31, 2014.

*Restricted Stock Units*

The Company may grant awards of restricted stock units ("RSUs") to non-employee directors, members of the management team and employees on a discretionary basis pursuant to the 2013 Plan. Each RSU entitles the holder to receive, at the end of each vesting period, a specified number of shares of the Company's common stock. The total number of unvested RSUs at December 31, 2014 was 10,000. The issued and outstanding RSUs vest on the first anniversary of the grant date.

The fair value of the RSUs granted in the year ended December 31, 2014 was approximately $0.5 million. No RSUs were granted in prior years. The Company recorded stock-based compensation expense related to RSUs of $0.1 million for the year ended December 31, 2014. No compensation expense related to RSUs was recorded in prior years. As of December 31, 2014, there was approximately $0.4 million of total unrecognized compensation expense related to RSUs, which is expected to be recognized over a period of nine months.

Unvested RSU activity for the year ended December 31, 2014 is summarized as follows:

| | |
|---|---|
| Unvested shares at December 31, 2013 | — |
| Granted | 10,000 |
| Vested | — |
| Unvested shares end of period | 10,000 |

*Restricted Stock and Early Exercise of Stock Options*

Certain employees were granted restricted stock and certain directors were permitted to early exercise their stock options, upon approval by the Company's Board, at which time the awards became subject to restricted stock agreements. These shares of restricted stock granted upon early exercise of the options are subject to the same vesting provisions as the original stock option awards. Accordingly, the Company has recorded the exercise proceeds from early exercises as a restricted stock liability in the consolidated balance sheets. The restricted stock liability is reclassified into stockholders' equity as the restricted stock and options vest.

Unvested restricted stock activity for the year ended December 31, 2014 is summarized as follows:

| | |
|---|---|
| Unvested shares at December 31, 2013 | 23,295 |
| Granted | — |
| Vested | (14,773) |
| Forfeited | — |
| Unvested shares at December 31, 2014 | 8,522 |

There were no shares of restricted stock granted during the years ended December 31, 2014 and 2013. The weighted-average purchase price of restricted stock granted during the year ended December 31, 2012 was $0.91. The fair value of awards vested during the years ended December 31, 2014, 2013 and 2012 was $0.7 million, $1.7 million and $0.5 million, respectively.

*Performance-Based Stock Option Grants*

During the year ended December 31, 2014, no options to purchase shares of common stock that contain performance-based or a combination of performance-based and service-based vesting criteria were granted by the Company. During the year ended December 31, 2013, the Company granted options to purchase 355,454 shares of common stock, which contain performance-based and service-based vesting criteria, to employees. Performance-based vesting criteria for these options primarily relate to milestone events specific to the Company's corporate goals, including but not limited to certain preclinical and clinical development milestones related to the Company's product candidates. Stock-based compensation expense associated with these performance-based stock options is recognized if the performance condition is considered probable of achievement using management's best estimates. As of December 31, 2014, certain of the performance-based milestones had been achieved and the achievement of certain other milestones have been deemed probable and therefore the related expense has either been fully recognized or is being recognized over the remaining service period. The achievement of the remaining milestones was deemed to be not probable as of December 31, 2014 and therefore no expense has been recognized related to these awards. During the years ended December 31, 2014 and 2013, the Company recognized stock-based compensation expense of $0.9 million, related to stock options with performance-based vesting criteria. No stock-based compensation expense related to stock options with performance-based criteria was recorded during the year ended December 31, 2012.

Agios Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (continued)

***Stock-Based Compensation Expense***

The fair value of each stock option granted to employees is estimated on the date of grant using the Black-Scholes option-pricing model. The following table summarizes the weighted average assumptions used in calculating the grant date fair value of the awards:

| | Years Ending December 31, | | |
|---|---|---|---|
| | **2014** | **2013** | **2012** |
| Risk-free interest rate | 1.83% | 1.31% | 1.09% |
| Expected dividend yield | — | — | — |
| Expected term (in years) | 6.03 | 6.42 | 6.08 |
| Expected volatility | 78.61% | 92.49% | 97.75% |

***Risk-Free Rate***

The risk-free rate is based on the yield curve of U.S. Treasury securities with periods commensurate with the expected term of the options being valued.

***Dividends***

The Company has never paid, and does not anticipate paying, any cash dividends in the foreseeable future, and therefore uses an expected dividend yield of zero in the option-pricing model.

***Volatility***

Since the Company was privately held through July 2013, it does not have the relevant company-specific historical data to support its expected volatility. As such, the Company has used a weighted-average of expected volatility based on the volatilities of a representative group of publicly-traded biopharmaceutical companies. For purposes of identifying representative companies, the Company considered characteristics such as number of product candidates in earlier stages of product development, area of therapeutic focus, length of trading history, companies' stage of life cycle, size, and relevant financial metrics. The expected volatility has been determined using a weighted-average of the historical volatilities of the representative group of companies for a period equal to the expected term of the option grant. The Company intends to continue to consistently apply this process using similar entities until a sufficient amount of historical information regarding the volatility of the Company's own share price becomes available or until circumstances change, such that the identified entities are no longer representative companies. In the latter case, more suitable, similar entities whose share prices are publicly available would be utilized in the calculation.

***Expected Term***

The Company uses the "simplified method" as prescribed by the Securities and Exchange Commission Staff Accounting Bulletin No. 107, *Share Based Payments*, to estimate the expected term of stock option grants. Under this approach, the weighted-average expected life is presumed to be the average of the contractual term (ten years) and the weighted-average vesting term of the Company's stock options, taking into consideration multiple vesting tranches. The Company utilizes this method due to lack of historical exercise data and the plain-vanilla nature of the Company's share-based awards.

***Forfeitures***

Forfeitures are required to be estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates. The Company based its estimate of forfeitures on data from a representative group of publicly-traded biopharmaceutical companies, as the Company does not currently have sufficient history, and records the stock-based compensation expense only on the awards that are expected to vest. To date forfeitures have been less than 5.0% of total grants.

**2013 Employee Stock Purchase Plan**

In June 2013, the Company's Board of Directors adopted, and in July 2013 the Company's stockholders approved, the 2013 Employee Stock Purchase Plan (the "2013 ESPP"). The 2013 ESPP will be administered by the Company's Board of Directors or by a committee appointed by the Company's Board of Directors. Under the 2013 ESPP, each offering period is six months, at the end of which employees may purchase shares of common stock through payroll deductions made over the term of the offering period. The per-share purchase price at the end of each offering period is equal to 85% of the closing price of one share of the Company's common stock at the beginning or end of the offering period, whichever is lower, subject to Internal Revenue Service limits. The first offering period was initiated on September 1, 2014. No shares were issued during the year ended December 31, 2014 under the 2013 ESPP. The 2013 ESPP initially provides participating employees with the opportunity to purchase up to an aggregate of 327,272 shares of the Company's common stock.

The Company recorded $0.1 million of stock-based compensation expense for the year ended December 31, 2014 related to the 2013 ESPP. No stock-based compensation expense related to the 2013 ESPP was recorded during the year ended December 31, 2013.

**10. Income Taxes**

The provision (benefit) for income taxes is as follows for the years ended December 31, 2014, 2013 and 2012 (in thousands):

| | Years Ended December 31, | | |
|---|---|---|---|
| | **2014** | **2013** | **2012** |
| Current: | | | |
| Federal | $ (444) | $ (3,263) | $(9,531) |
| State | 18 | — | — |
| Total current | (426) | (3,263) | (9,531) |
| Deferred: | | | |
| Federal | — | 3,842 | 6,707 |
| State | — | — | — |
| Total deferred | — | 3,842 | 6,707 |
| Total | $ (426) | $ 579 | $(2,824) |

Agios Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (continued)

A reconciliation of the expected income tax benefit (expense) computed using the federal statutory income tax rate to the Company's effective income tax rate is as follows for the years ended December 31, 2014, 2013 and 2012:

| | December 31, | | |
|---|---|---|---|
| | 2014 | 2013 | 2012 |
| Income tax benefit computed at federal statutory tax rate | 35.00% | 35.00% | 35.00% |
| State taxes, net of federal benefit | 4.90 | 4.02 | 7.07 |
| Change in valuation allowance | (35.80) | (38.02) | (28.08) |
| General business credits and other credits | (1.90) | 0.52 | 0.12 |
| Permanent differences | (2.10) | (1.75) | (0.63) |
| Interest and penalties | — | (1.19) | (1.95) |
| Other | 0.80 | (0.07) | 0.79 |
| Total | 0.90% | (1.49)% | 12.32% |

During the years ended December 31, 2013 and 2012, the Company incurred $0.6 million for interest and penalties related to the non-payment of U.S. federal income taxes, respectively. No interest and penalties were incurred during the year ended December 31, 2014.

Deferred income taxes reflect the net tax effects of temporary differences between the carrying amount of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. Significant components of the Company's deferred tax assets and liabilities for the years ended December 31, 2014 and 2013 are as follows (in thousands):

| | 2014 | 2013 |
|---|---|---|
| Deferred tax assets: | | |
| Net operating loss carryforwards | $ 53,545 | $ 21,901 |
| Deferred revenue | 8,713 | 23,171 |
| Tax credit carryforwards | 3,159 | 637 |
| Purchased intangible assets | 137 | 147 |
| Stock-based compensation | 3,461 | 768 |
| Deferred rent | 1,622 | 138 |
| Other | 325 | 231 |
| Total deferred tax assets | 70,962 | 46,993 |
| Valuation allowance | (69,433) | (46,549) |
| Total deferred tax assets | $ 1,529 | $ 444 |
| Deferred tax liabilities: | | |
| Depreciation and amortization | $ (1,529) | $ (444) |
| Total deferred tax liabilities | $ (1,529) | $ (444) |
| Net deferred tax asset | $ - | $ - |

As of December 31, 2014, the Company had net operating loss carryforwards available to reduce federal and state income taxes of approximately $166.9 million and $208.1 million, respectively. If not utilized, these

carryforwards expire at various dates through 2034. At December 31, 2014 the Company also has available research and development tax credits for federal and state income tax purposes of approximately $2.5 million and $1.1 million, respectively.

Utilization of the net operating loss carryforwards and credits may be subject to annual limitations as prescribed by federal and state statutory provisions. The annual limitation may result in the expiration of net operating loss carryforwards prior to its utilization.

The Company has federal and state net operating loss carry forward (NOLs) related to stock compensation in the amount of $39.1 million and $39.2 million, respectively, that is not included in deferred tax assets. When the excess stock-based compensation related to NOL carryover tax assets are realized, the benefit will be credited directly to stockholders' equity.

Utilization of the NOLs and tax credit carryforwards may be subject to a substantial annual limitation due to ownership change limitations that have occurred previously or that could occur in the future, as provided by Section 382 of the Internal Revenue Code of 1986 ("Section 382"), as well as similar state provisions. Ownership changes may limit the amount of NOLs and tax credit carryforwards that can be utilized annually to offset future taxable income and tax, respectively. In general, an ownership change, as defined by Section 382, results from transactions that increase the ownership of 5% shareholders in the stock of a corporation by more than 50 percent in the aggregate over a three-year period. During 2011, the Company completed a study through December 31, 2011, to determine whether any ownership change has occurred since the Company's formation and has determined that transactions have resulted in two ownership changes, as defined by Section 32. The impact of the ownership changes have been reflected in the Company's deferred tax assets in the table above. There could be additional ownership changes in the future that could further limit the amount of NOLs and tax credit carryforwards that the Company can utilize.

As required by ASC 740, management of the Company has evaluated the positive and negative evidence bearing upon the realizability of its deferred tax assets. During the year ended December 31, 2011, management determined that it was more likely than not that it would realize a portion of its deferred tax assets because of the Company's ability to carryback future losses for U.S. federal income tax purposes. As a result, the Company reversed approximately $10.7 million of the valuation allowance on its deferred tax assets in the year ended December 31, 2011, representing the amount of deferred tax assets that will be realized in 2012 and 2013, the years available for carryback. The Company utilized certain of the deferred tax assets, including net operating losses, generated in the year ended December 31, 2013 to reduce its federal income taxes payable in the years ended December 31, 2013 and 2012. For the remainder of the Company's deferred tax assets, management determined that it is more likely than not that the Company may not realize the benefit and has recorded a valuation allowance of approximately $69.4 million and $46.5 million at December 31, 2014 and 2013, respectively. The valuation allowance increased by $22.9 million in the year ended December 31, 2014.

The Company applies the accounting guidance in ASC 740 related to accounting for uncertainty in income taxes. The Company's reserves related to taxes are based on a determination of whether, and how much of, a tax benefit taken by the Company in its tax filings or positions is more likely than not to be realized following resolution of any potential contingencies present related to the tax benefit. As of December 31, 2014 and 2013 the Company had no unrecognized tax benefits. The Company recognizes interest and penalties related to uncertain tax positions in income tax expense.

The statute of limitations for assessment by the Internal Revenue Service (IRS) and state tax authorities is open for tax years ending December 31, 2014, 2013, 2012, 2011 and 2010 although carryforward attributes that were generated for tax years prior to 2010 may still be adjusted upon examination by the IRS or state tax authorities if they either have been, or will be, used in a future period. There are currently no federal or state audits in progress.

**11. Defined Contribution Benefit Plan**

The Company sponsors a 401(k) retirement plan, in which substantially all of its full-time employees are eligible to participate. Participants may contribute a percentage of their annual compensation to this plan, subject to statutory limitations. The Company did not provide any contributions to this plan during the years ended December 31, 2014, 2013 or 2012.

Beginning January 1, 2015, the Company will make matching contributions equal to 50% of the employee's contributions, subject to a maximum of 6% of eligible compensation.

**12. Selected Quarterly Financial Data (Unaudited)**

| 2014 | First Quarter | Second Quarter | Third Quarter | Fourth Quarter |
|---|---|---|---|---|
| | (In thousands, except per share data) | | | |
| Total revenue | $ 8,411 | $ 8,411 | $ 33,900 | $ 14,636 |
| Income (loss) from operations | (12,284) | (18,330) | 3,208 | (26,727) |
| Net income (loss) | (12,248) | (18,296) | 3,704 | (26,664) |
| Net income (loss) applicable to common stockholders | (12,248) | (18,296) | 3,704 | (26,664) |
| Net income (loss) per share applicable to common stockholders – basic | (0.39) | (0.54) | 0.11 | (0.76) |
| Net income (loss) per share applicable to common stockholders – diluted | (0.39) | (0.54) | 0.10 | (0.76) |

| 2013 | First Quarter | Second Quarter | Third Quarter | Fourth Quarter |
|---|---|---|---|---|
| | (In thousands, except per share data) | | | |
| Total revenue | $ 6,268 | $ 6,268 | $ 6,268 | $ 6,744 |
| Loss from operations | (7,046) | (8,526) | (11,069) | (12,242) |
| Net loss | (7,228) | (8,620) | (11,177) | (12,382) |
| Net loss applicable to common stockholders | (9,025) | (10,418) | (11,744) | (12,382) |
| Net loss per share applicable to common stockholders – basic and diluted | (2.47) | (2.80) | (0.52) | (0.40) |

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## EXHIBIT INDEX

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

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| Exhibit Number | Description of Exhibit | Incorporated by Reference | | | | Filed Herewith |
|---|---|---|---|---|---|---|
| | | Form | File Number | Date of Filing | Exhibit Number | |
| 10.11# | Letter of Agreement, dated May 4, 2010 between the Registrant and Glenn Goddard | S-1 | 333-189216 | June 10, 2013 | 10.11 | |
| 10.12 | Form of Indemnification Agreement between the Registrant and each of its Executive Officers and Directors | S-1 | 333-189216 | July 11, 2013 | 10.12 | |
| 10.13 | Lease, dated as of August 2, 2010, between the Registrant and Thirty-Eight Sidney Street Limited Partnership | S-1 | 333-189216 | June 10, 2013 | 10.12 | |
| 10.14† | Discovery and Development Collaboration and License Agreement, dated as of April 14, 2010, as amended on October 3, 2011, between the Registrant and Celgene Corporation | S-1 | 333-189216 | July 16, 2013 | 10.14 | |
| 10.15* | Third Amendment to Discovery and Development Collaboration and License Agreement, dated July 14, 2014 between the Registrant and Celgene Corporation | | | | | X |
| 10.16 | Common Stock Purchase Agreement, dated as of July 16, 2013, between the Registrant and Celgene Alpine Investment Co., LLC | S-1 | 333-189216 | July 16, 2013 | 10.15 | |
| 10.17 | Lease, dated as of September 15, 2014, between the Registrant and Forest City 88 Sidney, LLC | 8-K | 001-36014 | September 19, 2014 | 10.1 | |
| 10.18 | Termination of Lease, dated September 15, 2014, by and between Agios Pharmaceuticals, Inc. and 38 Sidney Street Limited Partnership | 8-K | 001-36014 | September 19, 2014 | 10.2 | |
| 10.19 | First Amendment to Lease, dated as of November 21, 2011, between the Registrant and Forest City 88 Sidney, LLC | 8-K | 001-36014 | November 26, 2014 | 10.1 | |

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| Exhibit Number | Description of Exhibit | Incorporated by Reference | | | | Filed Herewith |
|---|---|---|---|---|---|---|
| | | Form | File Number | Date of Filing | Exhibit Number | |
| 21.1 | Subsidiaries of the Registrant | S-1 | 333-189216 | June 10, 2013 | 21.1 | |
| 23.1 | Consent of Ernst & Young LLP | | | | | X |
| 31.1 | Certification of principal executive officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended | | | | | X |
| 31.2 | Certification of principal financial officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended. | | | | | X |
| 32.1 | Certification of principal executive officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002. | | | | | X |
| 32.2 | Certification of principal financial officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002. | | | | | X |
| 101.INS | XBRL Instance Document | | | | | X |
| 101.SCH | XBRL Taxonomy Extension Schema Document | | | | | X |
| 101.CAL | XBRL Taxonomy Calculation Linkbase Document | | | | | X |

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| Exhibit Number | Description of Exhibit | Incorporated by Reference | | | | Filed Herewith |
|---|---|---|---|---|---|---|
| | | Form | File Number | Date of Filing | Exhibit Number | |
| 101.DEF | XBRL Taxonomy Extension Definition Linkbase Document | | | | | X |
| 101.LAB | XBRL Taxonomy Label Linkbase Document | | | | | X |
| 101.PRE | XBRL Taxonomy Presentation Linkbase Document | | | | | X |

# Indicates management contract or compensatory plan or arrangement.
† Confidential treatment has been granted as to certain portions, which portions have been omitted and filed separately with the Securities and Exchange Commission.
* Confidental treatment has been requested as to certain portions, which portions have been omitted and filed separately with the Securities and Exchange Commisison.

**Exhibit 10.15**

Confidential Materials omitted and filed separately with the Securities and Exchange Commission.
[****] denotes omissions.

**THIRD AMENDMENT**
**TO**
**DISCOVERY AND DEVELOPMENT**
**COLLABORATION AND LICENSE AGREEMENT**

This Third Amendment to the Discovery and Development Collaboration and License Agreement (the "Third Amendment") is entered into as of July 14th, 2014 (the "Third Amendment Effective Date") by and between Agios Pharmaceuticals, Inc. ("Agios") and Celgene Corporation ("Celgene"). Agios and Celgene may each be referred to herein individually as a "Party" and collectively as the "Parties." Capitalized terms used in this Third Amendment and not otherwise defined herein shall have the meanings set forth in the Agreement. All references to Sections and Articles herein are references to Sections and Articles of the Agreement.

**INTRODUCTION**

A. Celgene and Agios are parties to that certain Discovery and Development Collaboration and License Agreement, dated April 14, 2010 and twice amended on October 3rd, 2011 (the "Agreement").

B. Pursuant to the Agreement, the Parties have engaged in a collaboration that applies Agios' expertise and technology to the discovery and validation of novel targets, primarily cancer metabolism targets, and the discovery and development of associated therapeutics, primarily in the Oncology Field, and provides for the development and commercialization of such therapeutics.

C. The Parties wish to amend the Agreement in order to allow more flexibility in the design and conduct of Phase I MAD Studies, and additional nonclinical and/or clinical activities that Agios agrees to perform at Celgene's request, by providing for Celgene to pay all Development Costs incurred by Agios in performing such activities at Celgene's request and clarifying the mechanism for payment of such Development Costs.

NOW, THEREFORE, in consideration of the covenants and agreements contained herein, and for other valuable consideration, the receipt and adequacy of which are hereby acknowledged, Agios and Celgene agree as follows:

1. Amendment of Section 1.48. Section 1.48 is hereby amended and restated in its entirety to read as follows:

"Development Cost Initiation Date" means (a) with respect to any Co-Commercialized Program for which Celgene exercises the Celgene Program Option at IND Acceptance, [****]; (b) with respect to any Co-Commercialized Program for which Celgene exercises the Celgene Program Option at Completion of Phase I MAD, [****]; (c) with respect to any Co-Commercialized Program for which Celgene exercises the Celgene Program Option early under Section 3.6(c), [****]; (d) with respect to a Buy-In Program, [****]; (e) with respect to any Picked Validated Program selected by Celgene, [****]; and (f) with respect to any Split Program, [****]

**2. Amendment of Section 2.4(a).** Section 2.4(a) is hereby amended to add the following to the end of such section:

In addition, if Celgene requests that Agios perform any Phase I MAD Study and additional activities pursuant to Section 3.6(b)(iii)(A)(2) with respect to a Development Candidate, the JDC shall have oversight over such Phase I MAD Study and such additional activities for such Development Candidate (and the related Discovery Program).

**3. Amendment of Section 2.8(b).** Section 2.8(b) is hereby amended to add Section 3.9(a) to the list of cross references in such Section 2.8(b), with "3.9(a)" being added between "2.9" and "3.10(e)".

**4. Amendment and Restatement of Section 3.6(b)(iii)(A)(2).** Section 3.6(b)(iii)(A)(2) is hereby amended and restated in its entirety to read as follows:

(2) Celgene, within such Celgene IND Option Exercise Period, may provide Agios written notice that Celgene elects that Agios conduct the first Phase I MAD Study for the Development Candidate. In such event, Agios shall be responsible for conducting the first Phase I MAD Study with respect to such Development Candidate under a protocol approved by the JDC by Mutual Consent that meets the Phase I MAD Protocol Criteria, and any additional clinical and/or nonclinical activities that Agios agrees to perform at Celgene's request, under a Development Plan (and pursuant to a Development Budget that has been approved by the JDC pursuant to Section 3.9(a)), and, unless the Program becomes a Split Program, Celgene shall be obligated to pay the Phase I Amount and the Development Costs with respect thereto pursuant to Section 9.4(a)(ii). Upon Agios' completion of such first Phase I MAD Study, Agios shall deliver to Celgene a final written report that meets the Phase I Report Criteria. Within [****] days of Celgene's receipt of such written report, Celgene may reasonably request that Agios provide additional information and access to records (to the extent available to Agios at such time and not yet disclosed to the JRC or JDC as part of the regular updates under Section 3.1 (b) or 3.8(c), or under Section 3.6(b)(ii) or this Section 3.6(b)(iii)) with respect to such Phase I MAD Study and with respect to other Development Candidates that are undergoing IND-Enabling Studies or are at a later stage of Development under a different Program. Within [****] days following the Completion of Phase I MAD (and any such additional information or access) (such period, as may be so extended, the "Celgene MAD Option Exercise Period"; either the "Celgene IND Option Exercise Period" or the "Celgene MAD Option Exercise Period" may be referred to as a "Celgene Option Exercise Period"), Celgene may provide Agios written notice of its election to exercise the Celgene Program Option, in which event the provisions of Section 3.6(b)(iv) shall apply;

**5. Amendment and Restatement of Section 3.9(a).** Section 3.9(a) is hereby amended and restated in its entirety to read as follows:

(a) The Development under each Co-Commercialized Program, Split Program, or Buy-In Program shall be governed by a Development Plan (the "Development Plan") that describes the proposed overall objectives of such Licensed Program, as well as the activities to be performed, the Party responsible for performance of an activity (which shall be as provided in Section 3.8), [****] budget of Development Costs ("Development Budget"), and anticipated timelines for performance; provided that the Development Budget will only be applicable for periods following the Development Cost Initiation Date for such Licensed Program. In addition, if Celgene requests that Agios perform any Development activities for a Celgene Picked Validated Program and Agios consents to perform such activities, or that Agios perform any Phase I MAD Study and additional activities pursuant to Section 3.6(b)(iii)(A)(2), such activities shall also be governed by a Development Plan, with Development Budget; provided that the Development Budget for any such Phase I MAD Study or additional activities pursuant to Section 3.6(b)(iii)(A)(2) must be approved by the JDC, except that Celgene shall have final decision-making authority with respect to any dispute regarding the Development Budget for any such Phase I MAD Study and additional activities for Co-Commercialized Programs.

**6. Amendment of Section 3.10(b)(ii).** Section 3.10(b)(ii) is hereby amended to add the following to the end of such section:

Notwithstanding the above, in the event a Phase I MAD Study under a Split Program includes a disease-specific expansion cohort, and [****], that the initial Phase I MAD study and the disease-specific expansion cohort shall support initiation of a subsequent pivotal clinical trial, the principal purpose of which (a) is designed to establish that the product has an acceptable safety and efficacy profile for its intended use, and to determine warnings, precautions, and adverse reactions that are associated with such product in the dosage range to be prescribed; and (b) is a registration trial intended to support a filing of an application for a Regulatory Approval for such compound in the US Territory (the "Pivotal Trial"), then upon the FPD under the Pivotal Trial, Celgene shall pay Agios a milestone payment in an amount equal to the lesser of (A) Ten Million Dollars (US$10,000,000) or (B) fifty percent (50%) of the costs and expenses for the disease-specific expansion cohort, including the analysis of clinical samples and clinical trial product supply that are actually incurred by or on behalf of Agios and specifically identifiable or specifically allocable to such disease-specific expansion cohort (the "Disease-Specific Expansion Cohort Milestone Payment"). Such Disease-Specific Expansion Cohort Milestone Payment shall be made within [****] days after Celgene's receipt of appropriate invoice. Unless otherwise agreed by the JDC by Mutual Consent, the maximum amount of Disease-Specific Expansion Cohort Milestone Payments payable under a Split Program will be Ten Million Dollars (US$10,000,000), regardless of the number of disease-specific expansion cohorts and Pivotal Trials under the Split Program.

In the event a Phase I MAD Study under a Split Program already includes a disease- specific expansion cohort, and the JDC by Mutual Consent agrees to amend the Phase I MAD Study to include a Phase II Study arm with a larger patient population in the same disease-specific indication, then the Development Cost Initiation Date shall begin upon [****].

**7. Amendment of Section 4.1(h).** Section 4.1(h) is hereby amended to append the following phrase at the end of the sentence: except to the extent such Manufacturing Costs are included in Development Costs payable by Celgene pursuant to Section 9.4(a)(ii) in connection with a Phase I MAD Study or additional activities performed by Agios pursuant to Section 3.6(b)(iii)(A)(2)".

**8. Amendment and Restatement of Section 9.3(a).** Section 9.3(a) is hereby amended and restated in its entirety to read as follows:

(a) Payments for Co-Commercialized Programs. Following Celgene's selection of a Development Candidate at the DC Selection Stage under a Co- Commercialized Program pursuant to Section 3.6(b), on a Program-by-Program basis, Celgene shall pay Agios Twenty-Two Million Five Hundred Thousand Dollars (US$22,500,000) (the "IND Amount") upon an IND Acceptance achieved by Agios for such Development Candidate in such Co-Commercialized Program pursuant to Section 3.6(b)(iii)(A); provided that (i) no such IND Amount will be due with respect to the first [****] IND Acceptances achieved by Agios under Co-Commercialized Programs for which IND Acceptance is achieved; (ii) no such IND Amount will be due prior to [****]; and (iii) no such IND Amount will be due with respect to any IND Acceptance achieved by Agios under an Optionable Program that becomes a Split Program pursuant to Section 3.10. For clarity, Celgene shall not owe the IND Amount with respect to any Picked Validated Program selected by Celgene or for any Buy-In Program (whether Celgene is the Buy-In Party or Agios is).

**9. Amendment and Restatement of Section 9.4(a).** Section 9.4(a) is hereby amended and restated in its entirety to read as follows:

(a) For Licensed Programs; Phase I MAD Study. Except as set forth in clauses (b) and (c) below with respect to Split Programs and Buy-In Programs, the following shall apply for Co-Commercialized Programs and Celgene Picked Validated Programs and for any Phase I MAD Study pursuant to Section 3.6(b)(iii)(A)(2):

(i) With respect to each Co-Commercialized Program and Picked Validated Program selected by Celgene under which Agios performs Development activities hereunder, Celgene shall be responsible for bearing one hundred percent (100%) of the Development Costs for such Licensed Program, including the Development Costs of any Clinical Trials or other Licensed Program activities conducted by Agios (at Celgene's request pursuant to Section 3.6(b)(iv)(B) and as agreed to by Agios), that (A) are incurred after the Development Cost Initiation Date for such Program and (B) are within [****] percent ([****]%) of the approved Development Budget

under the Development Plan for such Program. Notwithstanding anything herein to the contrary, any costs of the first Phase I MAD Study conducted by Agios, pursuant to Section 3.6(b)(iii)(A)(2)), shall not be included in the Development Costs under this Section 9.4(a)(i) but shall be addressed by Section 9.4(a)(ii).

(ii) If Celgene requests that Agios perform the first Phase I MAD Study and any additional activities pursuant to Section 3.6(b)(iii)(A)(2), unless the applicable Program becomes a Split Program, then upon the earlier of (I) determination of the first maximum tolerated dose for the Development Candidate by Agios (the "MTD Determination") or (II) the Option Exercise Date, Celgene shall pay Agios a milestone payment in an amount equal to the greater of (1) Five Million Dollars (US$5,000,000) or (2) one hundred percent (100%) of the Development Costs for such Phase I MAD Study conducted by Agios that (A) are incurred for any such Phase I MAD Study up to the earlier of the MTD Determination or the Option Exercise Date and (B) are within [****] percent ([****]%) of the approved Development Budget under the Development Plan for such Phase I MAD Study (the "Phase I Amount"). The Phase I Amount shall be payable within [****] days following the earlier of Celgene's receipt of a written notice of the MTD Determination or the Option Exercise Date. Subsequent to the earlier of the MTD Determination or the Option Exercise Date, Celgene shall be responsible for bearing one hundred percent (100%) of the Development Costs for remaining phase(s) of such Phase I MAD Study that (A) are incurred for any such Phase I MAD Study and (B) are within [****] percent ([****]%) of the approved Development Budget under the Development Plan for such Phase I MAD Study. For clarity, Celgene shall not be responsible for the Phase I Amount or the Development Costs of any Phase I MAD Study conducted by Agios, pursuant to Section 3.6(b)(iii)(A)(2)), with respect to any Split Program.

(iii) Within [****] days following the beginning of the [****] of each [****], Agios shall prepare and deliver to Celgene a [****] report detailing its Development Costs incurred during the [****] of such [****] and detailing a budget estimate ("Budget Estimate") for the remaining [****] of such [****], with respect to which Celgene is required to pay pursuant to Section 9.4(a)(i) or (ii). Agios shall submit any supporting information reasonably requested by Celgene related to such Development Costs included in Agios' report within [****] days after Agios' receipt of such request. Celgene shall pay all amounts of such Development Costs within [****] days following the later of Celgene's receipt of such report and Celgene's receipt of such supporting information. Within [****] days following the end of each [****], Agios shall prepare and deliver to Celgene a reconciliation report detailing the difference between its Development Costs incurred during the [****] of such [****], with respect to which Celgene is required to pay pursuant to Section 9.4(a)(i) or (ii), and the Budget Estimate for the same period. Agios shall submit any supporting information reasonably requested by Celgene related to such Development Costs included in Agios' reconciliation report within [****] days after Agios' receipt of such request. Celgene shall pay any unpaid amounts of any Development Costs identified in such reconciliation report within [****] days following the later of Celgene's receipt of such reconciliation report and Celgene's receipt of such supporting

information associated therewith. Any overpayment identified in such reconciliation report shall be credited towards the payment obligations of Celgene pursuant to Section 9.4(a)(i) or (ii) for the following Calendar Quarter.

**10. Additional Conforming Amendments.**

(a) Section 1.130 is hereby amended to replace the table row for "Phase I Amount" with the following:

"Phase I Amount 9.4(a)(ii)".

(b) Each reference in the Agreement to Section 9.3(a)(i) is hereby replaced with a reference to Section 9.3(a).

(c) Section 1.41 is hereby amended to replace the reference to Section 9.4(a)(ii) with a reference to Section 9.4(a)(iii).

**11. Incorporation.** Article XV is hereby incorporated *mutatis mutandis* into this Third Amendment

**12. Effect on Agreement.** Except as specifically amended by this Third Amendment, the Agreement will remain in full force and effect and is hereby ratified and confirmed. To the extent a conflict arises between the terms of the Agreement and this Third Amendment, the terms of this Third Amendment shall prevail but only to the extent necessary to accomplish their intended purpose.

**[*Remainder of Page Intentionally Left Blank*]**

IN WITNESS WHEREOF, the Parties have executed this Third Amendment as of the Third Amendment Effective Date.

AGIOS PHARMACEUTICALS, INC.

By: /s/ David P. Schenkein
Title: CEO

CELGENE CORPORATION

By: /s/ Thomas O. Daniel
Title: President R & ED

Celgene Legal: /s/ JMC

**Exhibit 23.1**

**CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM**

We consent to the incorporation by reference in the Registration Statements (Form S-8 Nos. 333-201796, 333-193802 and 333-190101 and Form S-3 No. 333-200822) of Agios Pharmaceuticals, Inc. of our reports dated February 24, 2015 with respect to the consolidated financial statements of Agios Pharmaceuticals, Inc. and the effectiveness of internal control over financial reporting of Agios Pharmaceuticals, Inc. included in this Annual Report (Form 10-K) for the year ended December 31, 2014.

/s/ Ernst & Young LLP

Boston, Massachusetts
February 24, 2015

**Exhibit 31.1**

**CERTIFICATION**

I, David P. Schenkein, certify that:

1. I have reviewed this Annual Report on Form 10-K of Agios Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 24, 2015

/s/ David P. Schenkein

David P. Schenkein
Chief Executive Officer
(principal executive officer)

**Exhibit 31.2**

**CERTIFICATION**

I, Glenn Goddard, certify that:

1. 1. I have reviewed this Annual Report on Form 10-K of Agios Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: February 24, 2015

/s/ Glenn Goddard

Glenn Goddard
Senior Vice President, Finance
(principal financial and accounting officer)

**Exhibit 32.1**

**CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,**
**AS ADOPTED PURSUANT TO**
**SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

In connection with this Annual Report on Form 10-K of Agios Pharmaceuticals, Inc. (the "Company") for the year ended December 31, 2014, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, David P. Schenkein, Chief Executive Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, that, to his knowledge on the date hereof:

(1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 24, 2015

/s/ David P. Schenkein

David P. Schenkein
Chief Executive Officer
(principal executive officer)

**Exhibit 32.2**

**CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,**
**AS ADOPTED PURSUANT TO**
**SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

In connection with this Annual Report on Form 10-K of Agios Pharmaceuticals, Inc. (the "Company") for the year ended December 31, 2014, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Glenn Goddard, Senior Vice President, Finance of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, that, to his knowledge on the date hereof:

(1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 24, 2015

/s/ Glenn Goddard

Glenn Goddard
Senior Vice President, Finance
(principal financial and accounting officer)