

**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, 2016**

**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**

*(State or other jurisdiction of  
incorporation or organization)*

**88 Sidney Street,  
Cambridge, MA**

*(Address of principal executive offices)*

**26-0662915**

*(IRS Employer  
Identification No.)*

**02139**

*(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
<b>Common Stock, Par Value \$0.001 per share</b>	<b>NASDAQ Global Select Market</b>

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  Smaller reporting company   
(Do not check if a 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, 2016 (based on the last reported sale price on the NASDAQ Global Select Market as of such date) was \$1,189,342,604.

As of February 14, 2017, there were 42,234,316 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 2017 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, 2016 are incorporated by reference into Part III of this Annual Report on Form 10-K to the extent stated herein.

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[Table of Contents](#)

**Table of contents**

		<b>Page</b>
	<b><u>PART I</u></b>	
Item 1.	<a href="#">Business</a>	2
Item 1A.	<a href="#">Risk Factors</a>	44
Item 1B.	<a href="#">Unresolved Staff Comments</a>	76
Item 2.	<a href="#">Properties</a>	76
Item 3.	<a href="#">Legal Proceedings</a>	76
Item 4.	<a href="#">Mine Safety Disclosures</a>	76
	<b><u>PART II</u></b>	
Item 5.	<a href="#">Market for Registrant’s Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities</a>	77
Item 6.	<a href="#">Selected Consolidated Financial Data</a>	79
Item 7.	<a href="#">Management’s Discussion and Analysis of Financial Condition and Results of Operations</a>	81
Item 7A.	<a href="#">Quantitative and Qualitative Disclosures about Market Risk</a>	101
Item 8.	<a href="#">Financial Statements and Supplementary Data</a>	101
Item 9.	<a href="#">Changes in and Disagreements with Accountants on Accounting and Financial Disclosure</a>	102
Item 9A.	<a href="#">Controls and Procedures</a>	102
Item 9B.	<a href="#">Other Information</a>	104
	<b><u>PART III</u></b>	
Item 10.	<a href="#">Directors, Executive Officers and Corporate Governance</a>	104
Item 11.	<a href="#">Executive Compensation</a>	104
Item 12.	<a href="#">Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters</a>	104
Item 13.	<a href="#">Certain Relationships and Related Transactions, and Director Independence</a>	104
Item 14.	<a href="#">Principal Accounting Fees and Services</a>	104
	<b><u>PART IV</u></b>	
Item 15.	<a href="#">Exhibits and Financial Statement Schedules</a>	105
Item 16.	<a href="#">Form 10-K Summary</a>	105

## PART I

### References to Agios

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

### Cautionary Note Regarding 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 revenue, 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 regarding:

- the initiation, timing, progress and results of current and future preclinical studies and clinical trials, and our research and development programs;
- the potential of IDH1/IDH2 and pyruvate kinase-R mutations and the methylthioadenosine phosphorylase pathway as therapeutic targets;
- the potential benefits of our product candidates targeting IDH1/IDH2 or pyruvate kinase-R mutations, including ivosidenib (AG-120), enasidenib, AG-881 and AG-348;
- our plans to develop and commercialize our product candidates;
- our collaborations with Celgene Corporation and related subsidiaries, or Celgene;
- 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 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.

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## [Table of Contents](#)

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 the fundamental transformation of patients' lives through scientific leadership in the fields of cancer and rare genetic metabolic disorders. We have 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. Our therapeutic areas of focus are cancer and rare genetic metabolic disorders, 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, we are seeking to unlock the biology of cellular metabolism as a platform to create transformative therapies. Our most advanced cancer product candidates are enasidenib and ivosidenib (AG-120), which target mutated isocitrate dehydrogenase 2 and 1, or IDH2 and IDH1, respectively, and AG-881, which targets both mutated IDH1 and mutated IDH2. These mutations are found in a wide range of hematological malignancies and solid tumors. The lead product candidate in our rare genetic metabolic disorder, or RGD, programs, 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.

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 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.

### **Our Strategy**

We aim to build a multi-product company, based on our expertise in cellular metabolism that discovers, develops and commercializes first- or 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 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.*

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## [Table of Contents](#)

- *Maintain a culture of incisive decision-making driven by deep scientific interrogation and “respectful irreverence.”*
- *Foster a 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, and our efforts in the field of metabolic immuno-oncology, or MIO, are focused on the research and development of immunotherapies against certain metabolic targets that exert their antitumor efficacy primarily via the immune system.

### ***Cancer and cancer metabolism***

Cancer is a disease characterized by unregulated cell growth. Cancer typically develops when the repair of genetic material in normal cells begins to fail and genes that regulate cell growth become disrupted. Carcinogens, or cancer causing agents, such as radiation, chemicals and hormones, can trigger changes to the genetic material of a cell, and typically prompt this disruption. Cells that have been disrupted may become cancerous, leading to changes in the cells’ DNA, and ultimately uncontrolled growth. Cancer cells can spread to other areas of the body, or metastasize, and form tumors, which can destroy normal tissue or organs. Risk factors for cancer include family history, age, diet, and exogenous factors, such as exposure to ultraviolet sunlight and smoking. Cancers can be classified in stages to document disease severity, measured in stages of I to IV, generally based on tumor size, involvement of lymph nodes, and metastases.

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

#### *Cytotoxic chemotherapies*

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

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## [Table of Contents](#)

### *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., Kadcyła®) 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.

### ***Metabolic immuno-oncology***

There is increasing evidence that cellular metabolism plays an important role in modulating key components of the immune system. One of our areas of focus is MIO, a developing field which aims to modulate the activity of relevant immune cells by targeting critical metabolic nodes, thereby, enhancing the immune mediated anti-tumor response. We are leveraging our proprietary metabolic, target discovery and validation platforms with the goal of unlocking promising targets in this field. The immune system's ability to attack tumors is highly regulated by cellular metabolism. We believe that the emerging field of MIO has great potential to provide novel insights and targets for cancer immunotherapy in solid and hematologic malignancies. Our efforts in the MIO field are governed by our 2016 global research and collaboration agreement with Celgene, described in more detail below.

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## [Table of Contents](#)

### ***Rare genetic metabolic disorders***

Rare genetic metabolic disorders, a subset of orphan genetic metabolic diseases, are a broad group of more than 600 rare 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 disorders of metabolism.

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, Myozyme® 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 based on genetic markers and/or metabolic biomarkers. 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, along with genetic markers, 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.

[Table of Contents](#)

We will generally progress our drug candidates forward into phase 1 clinical trials if we have the ability to select patients who are most likely to respond to a given therapy based on biomarkers, for example, genetic or metabolic markers. 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 genetic marker and/or 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 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 our most advanced product candidates as of February 1, 2017, each of which is described in further detail below:

CANDIDATE	INDICATION	EARLY STAGE CLINICAL DEVELOPMENT	LATE STAGE CLINICAL DEVELOPMENT	NDA SUBMITTED	PRIMARY COMMERCIAL RIGHTS
<b>Enasidenib</b> (IDH2 mutant inhibitor)	R/R AML	Phase 1/2		✓	  Agios U.S. Co-promotion and Royalty
	R/R AML	Phase 3 IDHIdentify			
	Frontline AML	Phase 1b 7+3 Combo			
	Frontline AML	Phase 1/2 VIDAZA® Combo			
<b>Ivosidenib (AG-120)</b> (IDH1 mutant inhibitor)	R/R AML	Phase 1			
	Frontline AML	Phase 1b 7+3 Combo			
	Frontline AML	Phase 1/2 VIDAZA® Combo			
	Solid Tumors	Phase 1			
	Cholangiocarcinoma	Phase 3 ClarIDHY			
<b>AG-881</b> (pan-IDH mutant inhibitor)	R/R AML	Phase 1			  Joint Worldwide Collaboration
	Solid Tumors	Phase 1			
<b>AG-348</b> (PKR activator)	PK Deficiency	Phase 2 DRIVE PK			

**Targeting Mutated 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 cycle 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 ( $\alpha$ -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

## [Table of Contents](#)

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.

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-hydroxyglutarate, or 2HG. We have shown 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 have shown that inhibition of these mutated proteins could lead to clinical benefit for the subset of cancer patients whose tumors carry these mutations. By reducing elevated 2HG levels, our IDH inhibitors reverse the block in cellular differentiation, allowing tumorous cells to differentiate into normally functioning cells in patients with acute myeloid leukemia, or AML. We have identified selective development candidates that separately target and inhibit the mutated forms of IDH1 and IDH2. To date, our clinical data with enasidenib and ivosidenib (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, normalization of cell counts and mutational clearance in the bone marrow and blood. This differentiation effect is distinct from that seen with traditional cytotoxic chemotherapeutics, which lead to cell death, commonly used to treat cancer.

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.

<b>Mutation</b>	<b>Indications</b>	<b>% with IDH mutations</b>
<b>IDH1</b>	Low grade glioma & 2ary Glioblastomas (GBM)	68-74
	Chondrosarcoma	40-52
	AML	6-10
	Myelodysplastic Syndromes (MDS) / Myeloproliferative neoplasms (MPN)	3
	Intrahepatic Cholangiocarcinoma	11-24
	Ollier/Maffucci	80
	Others* (colon, melanoma, lung, prostate)	1-3
<b>IDH2</b>	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

### **Enasidenib**

Enasidenib 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. In December 2016, our partner Celgene submitted a new drug application, or NDA, to the U.S. Food and Drug Administration, or FDA, for enasidenib in relapsed and/or refractory AML, or R/R AML. The NDA is based on data from the ongoing phase 1/2 study of enasidenib

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## [Table of Contents](#)

in patients with advanced hematologic malignancies with an IDH2 mutation. In June 2014, the FDA granted us orphan drug designation for enasidenib for treatment of patients with AML and in August 2014, we announced that the FDA granted fast track designation to enasidenib for treatment of patients with AML that harbor an IDH2 mutation. In April 2016, we and Celgene received European Medicines Agency, or EMA, orphan drug designation for enasidenib for the treatment of AML. We continue to evaluate enasidenib in clinical trials evaluating hematological cancers with IDH2 mutations. To date, all clinical data reported by us and Celgene in hematological cancers highlights that the mechanism of response is consistent with preclinical studies, including substantial reduction of plasma 2-hydroxygluturate, or 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.

Celgene maintains worldwide development and commercial rights to enasidenib and Celgene will fund the future development and commercialization costs related to this program. Under our collaboration agreement focused on cancer metabolism, or the 2010 Agreement, Celgene is responsible for all development costs for enasidenib, and we are eligible to receive up to \$120.0 million in milestone payments and a tiered royalty on any net sales of products containing enasidenib. In addition to contributing our scientific and translational expertise, we intend to continue to conduct some clinical development and regulatory activities within the enasidenib development program under the 2010 Agreement. We also have co-commercialization rights to provide up to one-third of the commercialization efforts and will be reimbursed for those efforts.

We and Celgene are evaluating enasidenib in the following clinical trials:

### *Phase 1/2 clinical trial*

Enasidenib is being evaluated in a phase 1/2 multicenter, open-label, clinical trial to assess the safety, clinical activity, and tolerability of enasidenib in patients with advanced hematologic malignancies with an IDH2 mutation. The trial includes a dose-escalation phase and the following five expansion cohorts, all of which have completed accrual: (i) a cohort of 25 patients aged 60 years or older with IDH2 mutant-positive R/R AML, or any IDH2-mutant positive AML patient, regardless of age, who has relapsed following a bone marrow transplant, or BMT; (ii) a cohort of 25 patients aged less than 60 years with IDH2 mutant-positive R/R AML, not including patients with AML who have relapsed following a BMT; (iii) a cohort of 25 patients aged 60 years or older with untreated IDH2 mutant-positive AML who decline standard of care chemotherapy; (iv) a cohort of 25 patients with IDH2 mutant-positive advanced hematologic malignancies not eligible for cohorts for the previous three cohorts; and (v) a cohort of approximately 125 patients with IDH2 mutant-positive AML who are in second or later relapse, refractory to second-line induction or reinduction treatment, or have relapsed after allogeneic transplantation.

In December 2015, we reported clinical data, as of September 1, 2015, from the dose escalation phase and expansion cohorts of this trial, which included 209 response-evaluable enrolled patients with IDH2 mutant-positive AML. The data were presented at the 2015 American Society of Hematology Annual Meeting and Exposition in Orlando, Florida, or ASH 2015, and showed investigator-assessed objective responses in 79 out of 209 response-evaluable patients. Of the 79 patients who achieved an objective response, there were 37 complete remissions (CR), three complete remissions with incomplete platelet recovery (CRp), 14 marrow complete remissions (mCR), three complete remissions with incomplete hematologic recovery (CRi) and 22 partial remissions (PR). A CR 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 CRp 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 mCR means that there is no evidence for leukemia in the marrow but the blood counts have not fully restored. A CRi means there is no evidence for leukemia in the marrow but the neutrophils, a subset of white blood cells responsible for fighting bacterial infections, are outside the normal range. A PR 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. Of the

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## [Table of Contents](#)

159 patients with R/R AML, 59 achieved an objective response, including 29 CRs, one CRp, nine mCRs, three CRis and 17 PRs. Of the 24 patients with AML who declined standard of care chemotherapy, 10 achieved an objective response, including four CRs, one CRp, one mCR and four PRs. Of the 14 patients with myelodysplastic syndromes, or MDS, seven achieved an objective response, including three CRs, one CRp and three mCRs. Responding R/R AML patients were on the trial for up to 18 months with a median duration of treatment of 6.8 months, ranging from 1.8 to 18 months. Responses were durable, with median response duration of 6.9 months in patients with R/R AML. A safety analysis was conducted for all 231 treated patients. The majority of adverse events, or AEs, reported by investigators were mild to moderate, with the most common being nausea, diarrhea, fatigue and febrile neutropenia. The serious adverse events, or SAEs, observed during the trial were mainly disease related. Twenty-three percent of patients had treatment-related SAEs, including notably differentiation syndrome (4 percent), leukocytosis (4 percent) and nausea (2 percent). Drug-related Grade 5 SAEs included atrial flutter (one patient), cardiac tamponade (one patient), pericardial effusion (one patient) and respiratory failure (one patient). Dose escalation has been completed and a maximum tolerated dose, or MTD, has not been reached. Enasidenib continued to show favorable drug exposure and pharmacokinetics at all doses tested with substantial reductions in plasma levels of 2HG, which is produced by the mutated IDH2 and IDH1 proteins, to the level observed in healthy volunteers.

Together with Celgene, we presented clinical data from a subset of patients with MDS from the dose-escalation and expansion portions of this trial at the 2016 American Society of Hematology Annual Meeting and Exposition in San Diego, California, or ASH 2016, in December 2016. Among the 17 evaluable patients, the overall response rate was 59%, 10 of 17 patients, including one CR. Overall response rate reflects the best response achieved by patients, and includes CR, PR, mCR and any hematologic improvement, or HI. Of the 13 evaluable patients who had received prior treatment with a hypomethylating agent, seven had a response with enasidenib. Of the four patients with no prior treatment for MDS, two responded. And two patients experienced disease progression. Median overall survival was not reached after a median follow-up of 7.5 months.

### *IDHENTIFY*

Enasidenib is being evaluated in IDHENTIFY, an international phase 3, multi-center, open-label, randomized clinical trial designed to compare the efficacy and safety of enasidenib versus conventional care regimens in patients 60 years or older with IDH2 mutant-positive AML that is refractory to or relapsed after second- or third-line therapy. In January 2016, in conjunction with the initiation of the IDHENTIFY clinical trial, we received a milestone payment of \$25.0 million from Celgene pursuant to the 2010 Agreement.

This trial is currently enrolling patients and we have not yet presented any clinical data from this trial.

### *Phase 1b frontline combination trial*

Enasidenib is being evaluated in a phase 1b, multicenter, international, open-label clinical trial to evaluate the safety and clinical activity of enasidenib or ivosidenib (AG-120) in combination with induction and consolidation therapy in patients with newly diagnosed AML with an IDH2 or IDH1 mutation who are eligible for intensive chemotherapy. The trial will evaluate continuous dosing for up to one year with enasidenib administered at an initial oral dose of 100 mg once daily in patients with an IDH2 mutation or ivosidenib (AG-120) administered at an initial oral dose of 500 mg once daily in patients with an IDH1 mutation. Enasidenib or ivosidenib (AG-120) will be administered with two types of AML induction therapies (cytarabine with either daunorubicin or idarubicin) and two types of AML consolidation therapies (mitoxantrone with etoposide [ME] or cytarabine).

The trial is currently enrolling patients and we have not yet presented any clinical data from this trial.

### *Phase 1/2 frontline combination trial*

Enasidenib is being evaluated in a phase 1/2 frontline combination clinical trial, conducted by Celgene, of either enasidenib or ivosidenib (AG-120) in combination with VIDAZA® (azacitidine) in newly diagnosed AML

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## [Table of Contents](#)

patients not eligible for intensive chemotherapy, with a phase 1 component to determine the safety of the combinations, followed by a phase 2 randomized component evaluating the safety and clinical activity of each investigational combination versus single-agent VIDAZA® using a primary endpoint of overall response rate.

The trial has completed the phase 1 component and is currently enrolling in the phase 2 component and we have not yet presented any clinical data from this trial.

### ***Ivosidenib (AG-120)***

Ivosidenib (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, cholangiocarcinoma and glioma where both the treatment options and prognosis for patients are poor. On May 18, 2015, we announced that the FDA granted fast track designation to ivosidenib (AG-120) for treatment of patients with AML that harbor an IDH1 mutation. On June 10, 2015, the FDA granted us orphan drug designation for ivosidenib (AG-120) for treatment of patients with AML. In November 2016, the FDA granted fast-track designation to ivosidenib (AG-120) for treatment of patients with previously treated, unresectable or metastatic cholangiocarcinoma with and IDH1 mutation. In January 2017, we announced that we intend to submit an NDA to the FDA for ivosidenib (AG-120) in R/R AML by end of 2017.

We are evaluating ivosidenib (AG-120) in the following clinical trials:

#### *Phase 1 clinical trial (advanced hematologic malignancies)*

Ivosidenib (AG-120) is being evaluated in a phase 1 multicenter, open-label, dose-escalation and expansion clinical trial, designed to assess its safety, clinical activity and tolerability as a single agent in patients with advanced hematologic malignancies with an IDH1 mutation. Four expansion cohorts have been added to the trial. The first cohort will evaluate 125 AML patients who are in second or later relapse, are refractory to second-line induction or reinduction treatment, or have relapsed after allogeneic transplantation. The second cohort will evaluate 25 untreated AML patients. The third cohort will evaluate 25 patients with other non-AML IDH1 mutant-positive relapsed or refractory advanced hematologic malignancies. The fourth cohort will evaluate patients with relapsed IDH1 mutant-positive AML not eligible for the first arm or standard of care chemotherapy. Ivosidenib (AG-120) is administered at a 500 mg once daily oral dose, in 28-day cycles.

In December 2016, we presented clinical data from 78 patients treated with ivosidenib (AG-120) in the completed dose escalation portion of the ongoing phase 1 study of ivosidenib (AG-120) in advanced hematologic malignancies at ASH 2016. Doses were administered from 200 mg to 1,200 mg total daily doses. As of the August 1, 2016 data cut-off, seven patients (9%) remained on treatment. The median age of these patients was 68 (ranging from 36-89). Patients received a median of two prior chemotherapy regimens (ranging from zero to five). A safety analysis conducted for all 78 treated patients as of the data cut-off shows that ivosidenib (AG-120) continues to demonstrate a favorable safety profile. The majority of AEs reported by investigators were mild to moderate, with the most common regardless of causality being fatigue, nausea, diarrhea, pyrexia and peripheral edema. Fifty-three patients experienced at least one SAE, the majority being disease related. The maximum tolerated dose was not reached. The recommended phase 2 dose was 500 mg once daily, which is being studied in the ongoing expansion phase of the trial. Nine patients discontinued from the study due to death, including one reported as possibly related to ivosidenib (AG-120). All-cause mortality at 30 and 60 days was 12% and 21%, respectively. Thirty out of 78 treated patients achieved investigator-assessed objective responses for an overall response rate of 38%. Of the 30 patients who achieved an objective response, there were 14 (18%) CRs, eight CRi/CRp, six mCRs/morphologic leukemia-free state (MLFS) and two PRs. Of the 63 patients with R/R AML, 21 (33%) achieved an objective response, including 10 (16%) CRs, eight CRi/CRp, two MLFS and one PR. Responses were durable, with a median response duration of 10.2 months (3.7- not estimable (NE)) overall and 6.5 months (3.7-NE) in the subset of patients with R/R AML. Median duration of treatment is 3.2 months

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## [Table of Contents](#)

(ranging from 0.1 to 24.2 months). Longitudinal mutant IDH1 variant allele frequency data were reported for 67 patients. Patients with IDH1 mutational clearance, or IDH1-MC, were defined as having mutant IDH1 detected at screening (any sample type) and no reported mutant IDH1 in at least one on-study time point (FoundationOne® Heme sensitivity of 1%). IDH1-MC was observed in 36% of CRs (5 of 14) and 4% of non-CRs (2 of 53). IDH1-MC was enriched in patients achieving CR (p-value = .003). The median time to mutational clearance was 2.7 months (ranging from 1.1 to 3.8 months). This is the first demonstration that treatment with single agent ivosidenib (AG-120) can result in mutant IDH1 clearance. We are continuing to study the potential relationship between IDH1-MC and clinical benefit for patients with AML.

### *Phase 1 clinical trial (advanced solid tumors)*

Ivosidenib (AG-120) is being evaluated in a phase 1 multicenter, open-label, dose-escalation and expansion clinical trial, designed to assess its safety, clinical activity and tolerability as a single agent in patients with advanced solid tumors with an IDH1 mutation, including glioma, intrahepatic cholangiocarcinoma, or IHCC, and chondrosarcomas. Enrollment is now complete for four expansion cohorts of 25 patients each in (i) low grade glioma with at least six months of prior scans to assess volumetric changes, (ii) second-line cholangiocarcinoma, (iii) high grade, or metastatic, chondrosarcoma, and (iv) other solid tumors with an IDH1 mutation, who will receive the recommended dose of 500 mg of ivosidenib (AG-120) once daily.

In November 2015, we reported clinical data from the dose-escalation portion of our ongoing phase 1 clinical trial evaluating ivosidenib (AG-120) in patients with IDH1 mutant-positive advanced solid tumors who received ivosidenib (AG-120) administered from 200 mg to 1200 mg total daily doses. The data were presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics in Boston. As of the September 3, 2015 data cut-off, 29 of 55 patients with IDH1 mutant-positive advanced solid tumors had stable disease with one PR. Treatment with ivosidenib (AG-120) showed substantial reduction of 2HG in plasma and tumor tissue. Ivosidenib (AG-120) was well tolerated, with the majority of AEs reported by investigators being mild to moderate. The most common investigator-reported AEs were nausea, diarrhea, vomiting, anemia and QT prolongation. The majority of reported SAEs were disease related.

In November 2016, we reported initial data from the dose expansion cohort of our ongoing phase 1 clinical trial evaluating ivosidenib (AG-120) in patients with IDH1 mutant-positive glioma at the Society for Neuro-Oncology Annual Meeting in Scottsdale, Arizona. As of the August 1, 2016 data cut off, 66 patients had been treated with single agent ivosidenib (AG-120), and 28 patients (42%) remained on treatment. Data reported were from 20 patients who received ivosidenib (AG-120) administered from 200 mg to 1200 mg total daily doses in the dose-escalation phase, and 46 patients who received 500 mg daily doses of ivosidenib (AG-120) administered in two expansion cohorts, including 24 patients enrolled in a cohort with non-enhancing glioma and 22 glioma patients with enhancing disease enrolled in a basket cohort. The median age of these patients is 41 (ranging from 21-71). The median number of prior therapies was two (ranging from one to six) and included temozolomide (71%). Seventy-four percent of patients received radiotherapy. A safety analysis conducted for all 66 treated patients as of the data cut-off demonstrated that ivosidenib (AG-120) was well-tolerated with a favorable safety profile in glioma patients. No dose limiting toxicities were observed, and the majority of AEs reported by investigators were mild to moderate, with the most common being headache, nausea, diarrhea and vomiting. There were 11 patients with SAEs and none of them were determined to be drug-related. Efficacy data from 65 response-evaluable patients as of the data cut-off showed two patients had a minor response according to the Response Assessment in Neuro-Oncology for low grade glioma (RANO-LGG), and 41 (63%) patients had stable disease, including 27 with non-enhancing disease. The median treatment duration for non-enhancing glioma was 8.1 months (ranging from 1.4–17.8 months). Volumetric analysis conducted centrally demonstrated stabilization or a decrease in tumor growth rate compared to the pretreatment rate in 64% (14 of 22) of glioma patients with non-enhancing disease receiving ivosidenib (AG-120) and requires further development as a response evaluation tool.

Also in November 2016, we reported initial data from the dose expansion cohort of our ongoing phase 1 clinical trial evaluating ivosidenib (AG-120) in patients with IDH1 mutant-positive chondrosarcoma at the annual

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## [Table of Contents](#)

meeting of the Connective Tissue Oncology Society, or CTOS, in Lisbon, Portugal. The data presented at CTOS were from 21 chondrosarcoma patients as of September 23, 2016, 12 in the dose escalation cohort and nine in the expansion cohort, of which 7 remained on treatment. Doses received were 100 mg twice daily, and 300, 400, 500, 600, 800, 900 or 1200 mg once a day. Expansion cohort patients received 500 mg once a day. Median treatment duration was 2.6 months (ranging from 0.0–24.4 months). Prior therapy included surgery (57%), radiotherapy (33%) and chemotherapy (24%). The median number of prior systemic therapies was one (ranging from one to five). No dose-limiting toxicities were reported, and the majority of AEs reported by investigators were mild to moderate, with the most common being diarrhea, nausea, decreased appetite, QT prolongation and fatigue. Most SAEs were considered unrelated to treatment with one case of hypophosphatemia (low phosphorous blood level) considered to be possibly related to treatment. Of 20 response-evaluable patients, 11 (55%) experienced stable disease as their best response. The three-month progression-free survival rate was 58%. Baseline plasma levels of 2HG were elevated above the healthy volunteer range. Treatment with ivosidenib (AG-120) resulted in significant reduction of plasma 2HG compared to baseline. Up to 99.7% tissue 2HG reduction was documented in paired biopsies obtained from three patients treated with ivosidenib (AG-120). Together these data indicate the on-target pharmacodynamic effects of ivosidenib (AG-120).

### *ClarIDHy*

Ivosidenib (AG-120) is being evaluated in ClarIDHy, a registration-enabling phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial of ivosidenib (AG-120) in previously-treated patients with nonresectable or metastatic cholangiocarcinoma with an IDH1 mutation. The trial was initiated in December of 2016.

The trial is currently enrolling patients and we have not yet presented any clinical data from this trial.

### *Phase 1b frontline combination trial*

Ivosidenib (AG-120) is being evaluated in a phase 1b, multicenter, international, open-label clinical trial to evaluate the safety and clinical activity of enasidenib or ivosidenib (AG-120) in combination with induction and consolidation therapy in patients with newly diagnosed AML with an IDH2 or IDH1 mutation who are eligible for intensive chemotherapy. The trial is evaluating continuous dosing for up to one year with enasidenib administered at an initial oral dose of 100 mg once daily in patients with an IDH2 mutation or ivosidenib (AG-120) administered at an initial oral dose of 500 mg once daily in patients with an IDH1 mutation. Enasidenib or ivosidenib (AG-120) will be administered with two types of AML induction therapies (cytarabine with either daunorubicin or idarubicin) and two types of AML consolidation therapies (mitoxantrone with etoposide [ME] or cytarabine).

The trial is currently enrolling patients and we have not yet presented any clinical data from this trial.

### *Phase 1/2 frontline combination trial*

Ivosidenib (AG-120) is being evaluated in a phase 1/2 frontline combination clinical trial, conducted by Celgene, of either enasidenib or ivosidenib (AG-120) in combination with VIDAZA® (azacitidine) in newly diagnosed AML patients not eligible for intensive chemotherapy. The phase 1 component will determine the safety of the combinations, followed by a phase 2 randomized component evaluating the safety and clinical activity of each investigational combination versus single-agent VIDAZA® using a primary endpoint of overall response rate.

The trial has completed the phase 1 component and is currently enrolling in the phase 2 component and we have not yet presented any clinical data from this trial.

### *AGILE*

In the first half of 2017, we intend to initiate AGILE, a global, registration-enabling phase 3 clinical trial combining ivosidenib (AG-120) and VIDAZA® in newly diagnosed AML patients with an IDH1 mutation ineligible for intensive chemotherapy.

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## [Table of Contents](#)

As described below under “Collaborations with Celgene”, Celgene and we agreed to terminate the 2010 Agreement, effective as of August 15, 2016, as to the program directed to the IDH1 target, for which ivosidenib (AG-120) is the lead development candidate. Under the 2010 Agreement, Celgene had held development and commercialization rights to the IDH1 program outside of the United States, and we had held such rights inside the United States. As a result of the termination, we obtained global development and commercial rights to ivosidenib (AG-120) and the IDH1 program and expect to fund the future development and commercialization costs related to the program. Neither party will have any further financial obligations, including royalties or milestone payments, to the other concerning ivosidenib (AG-120) or the IDH1 program.

### ***AG-881: brain penetrant pan-IDH program***

AG-881 is an orally available, selective, brain-penetrant, pan-IDH mutant inhibitor, which provides added flexibility to our current portfolio of IDH mutant inhibitors. We and Celgene are jointly collaborating on a worldwide development program, wherein we share worldwide development costs and profits and Celgene would book any worldwide commercial sales. We will lead commercialization in the United States with both companies sharing equally in field-based commercial activities, and Celgene will lead commercialization outside of the United States with us providing one third of field-based commercial activities in the major EU markets. Under the AG-881 Agreements, we are eligible to receive up to \$70.0 million in potential milestone payments related to AG-881. We may also receive royalties at tiered, low- to mid-teen percentage rates on net sales if we elect to not participate in the development and commercialization of AG-881.

We are conducting two phase 1 multi-center, open-label clinical trials of AG-881, one in patients with advanced IDH1 or IDH2 mutant-positive solid tumors, including glioma, and the other in patients with advanced IDH1 or IDH2 mutant-positive hematologic malignancies whose cancer has progressed on a prior IDH inhibitor therapy. The goal of these trials is to evaluate the safety, pharmacokinetics, pharmacodynamics and clinical activity of AG-881 in advanced solid tumors and hematologic malignancies, respectively. In each trial, AG-881 will be administered continuously as a single agent dosed orally in a 28-day cycle. The first portion of each trial includes a dose-escalation phase in which cohorts of patients will receive ascending oral doses of AG-881 to determine the maximum tolerated dose and/or the recommended phase 2 dose based on safety and tolerability. The second portion of each trial is a dose expansion phase where patients will receive AG-881 to further evaluate the safety, tolerability and clinical activity of the recommended phase 2 dose.

The phase 1 trial in patients with advanced IDH1 or IDH2 mutant-positive hematologic malignancies has completed its dose escalation portion, establishing proof of mechanism as measured by reductions in 2HG levels, and is now closed for enrollment. No MTD was reached. In the phase 1 trial in IDH1 or IDH2 mutant-positive advanced solid tumors, an MTD was established and additional patients are now being enrolled for additional safety, pharmacokinetics and pharmacodynamics analyses.

We have not yet presented any clinical data from these trials.

### **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. PK deficiency is an autosomal recessive disease whereby all patients inherit two mutations, one from each parent and more than 250 different mutations have been identified to date. As a result, there are many different possible mutant combinations and no one clear mutational profile. Children with the disease produce PKR enzyme that

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## [Table of Contents](#)

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 the prevalence of PK deficiency is between approximately 1-in-20,000 and 1-in-485,000 people, 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. PK deficiency is an autosomal recessive disease whereby all patients inherit two mutations, one from each parent. More than 250 different mutations have been identified to date. The mutations observed in PK deficiency patients are classified in two main categories. A missense mutation causes a single amino acid change in the protein, generally resulting in some functional protein in the red blood cells. A non-missense mutation is any mutation other than a missense mutation, generally resulting in little functional protein in the red blood cells. It is estimated that 53 percent of patients with PK deficiency have two missense mutations, 25 percent have one missense and one non-missense mutation, and 22 percent have two non-missense mutations. Boston Children’s Hospital, in collaboration with us, is conducting a Natural History Study to better understand the symptoms and complications of PK deficiency, identify patients and treatment centers, and capture other clinical data, including genetic information.

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

AG-348 is an orally available small molecule and a potent activator of the wild-type (normal) and mutated PKR enzyme, which has resulted in restoration of adenosine triphosphate, or ATP, levels and a decrease in 2,3-diphosphoglycerate, or 2,3-DPG, levels in blood sampled from patients with PK deficiency and treated ex-vivo with AG-348. The wild-type PKR activity of AG-348 allowed 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. On March 24, 2015, the FDA granted us orphan drug designation for AG-348 for treatment of patients with PK deficiency. In December 2016, we announced our decision to advance AG-348 into pivotal development for PK deficiency.

#### *DRIVE-PK*

In June 2015, we initiated DRIVE PK, a global phase 2, first-in-patient, open-label safety and efficacy clinical trial of AG-348 in adult, transfusion-independent patients with PK deficiency. The multi-center, randomized trial includes two arms with up to 25 patients each. The patients in the first arm receive 50 mg twice daily, and the patients in the second arm receive 300 mg twice daily. The trial includes a 24 week treatment period with the opportunity for continued treatment beyond 24 weeks based on safety and clinical activity.

In June 2016, we reported the first clinical data from DRIVE PK at the 21<sup>st</sup> Congress of the European Hematology Association in Copenhagen, Denmark, establishing proof of concept for AG-348 as a novel, first-in-class, oral activator of both wild-type and mutated PKR enzymes.

In December 2016, we reported updated data from DRIVE PK at ASH 2016. At the time of the data presentation, the target enrollment for DRIVE PK had been reached with a total of 52 patients enrolled. As of the September 23, 2016 data cut-off, 34 patients had been treated in the study and were included in the safety analysis and 32 patients with at least 3 weeks of data were included in the efficacy analysis. Seventeen patients completed the initial 24 week treatment period, and as of the data cut-off, 15 patients remained on drug in the extension phase. In the 32 patients for whom efficacy could be evaluated, the mean baseline Hb was 9.2 g/dL. Twenty-eight of the 34 patients (82%) had been splenectomized prior to study entry. A safety analysis was conducted based on all 34 treated patients as of the data cut-off. AG-348 was well-tolerated, and the majority of

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## [Table of Contents](#)

treatment-related AEs were Grade 1-2; the most frequent being headache, nausea and insomnia. Two patients experienced SAEs including one Grade 2 AE of osteoporosis that was previously reported in a patient with osteopenia at baseline assessment. One patient experienced withdrawal hemolysis and anemia after AG-348 was temporarily discontinued due to a rapid treatment-related Hb increase, but stayed in the study and continued to receive treatment with AG-348 at a lower dose. Sex steroids were assessed at baseline, week 12 and week 24 for male and female patients. Increases in free testosterone and decreases in estradiol indicate aromatase inhibition by AG-348. Bone density scan data (n = 17) show high variability and are inconclusive. Clinical significance of the aromatase inhibition remains unclear. In the efficacy analysis, 15 of 32 total evaluable patients achieved rapid, robust and sustained Hb increases from baseline of greater than 1.0 g/dL as of the data cut-off. In patients who had Hb increases of greater than 1.0 g/dL, the mean maximum hemoglobin increase was 3.6 g/dL (range 1.2–5.2 g/dL). The median time to a Hb increase of greater than 1.0 g/dL was 1.4 weeks (range 1.1–21.0 weeks). Further data are needed to obtain a greater understanding of the relationship between genotype and response. Preliminary observations show that of the 26 evaluable patients with at least one missense mutation, 15 had shown an increase in Hb of greater 1.0 g/dL, while none of the six patients with two non-missense mutations showed increases in Hb of greater than 1.0 g/dL. Five patients homozygous for R479H (missense-missense) were also non-responders. Additional studies were conducted on blood samples of eight DRIVE PK patients. In this subset, four patients who had Hb level increases of greater than 1.0 g/dL on AG-348 experienced a greater than 50% average increase in the rate of metabolism of the PKR pathway. None of the four patients with less than a 1.0 g/dL increase in Hb experienced significant metabolic changes.

We have worldwide development and commercial rights to AG-348 and expect to fund the future development and commercialization costs related to this program. In December 2016, we announced that we plan to advance AG-348 into pivotal development as the first potential disease-modifying treatment for PK deficiency.

### ***AG-519***

AG-519 is an orally available small molecule and is a potent activator of the PKR enzyme, with comparable biochemical, cellular and in-vivo activity to AG-348, and was developed as our second PKR activator. We were evaluating AG-519 in a placebo-controlled phase 1 integrated single ascending dose and multiple ascending dose clinical trial in healthy volunteers. In December 2016, we announced that we are no longer developing our second PKR activator, AG-519, and withdrew our investigational new drug application, or IND, for AG-519, following a verbal notification of a clinical hold from the FDA.

## **Collaborations with Celgene**

### ***2016 Agreement***

On May 17, 2016, we entered into a master research and collaboration agreement, or the 2016 Agreement, with Celgene and its wholly owned subsidiary, Celgene RIVOT Ltd. The 2016 Agreement establishes a new global collaboration focused on the research and development of immunotherapies against certain metabolic targets that exert their antitumor efficacy primarily via the immune system. In addition to new programs identified under the 2016 Agreement, the parties have also agreed that all future development and commercialization of two remaining cancer metabolism programs discovered under the 2010 Agreement, including a program focused on methylthioadenosine phosphorylase, or MTAP, deleted cancers, will now be governed by the 2016 Agreement.

During the research term of the 2016 Agreement, we plan to conduct research programs focused on discovering compounds that are active against metabolic targets in the immuno-oncology, or IO, field. The initial four-year research term will expire on May 17, 2020. The research term may be extended for up to two or, in specified cases, up to four additional one-year terms.

For each program under the 2016 Agreement, we may nominate compounds that meet specified criteria as development candidates and, in limited circumstances, Celgene may also nominate compounds as development candidates for each such program. Celgene may designate the applicable program for further development following any such nomination, after which we may conduct, at our expense, additional pre-clinical and clinical development for such program through completion of an initial phase 1 dose escalation study.

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## [Table of Contents](#)

At the end of the research term, Celgene may designate for continued development up to three research programs for which development candidates have yet to be nominated, which are referred to as continuation programs. We may conduct further research and pre-clinical and clinical development activities on any continuation program, at our expense, through completion of an initial phase 1 dose escalation study.

We have granted Celgene the right to obtain exclusive options to development and commercialization rights for each program that Celgene has designated for further development and for each continuation program. Celgene may exercise each such option beginning on the designation of a development candidate for such program (or upon the designation of such program as a continuation program) and ending on the earlier of the end of a specified period after Celgene is furnished with specified information about the initial phase 1 dose escalation study for such program, or January 1, 2030. Research programs that have applications in the inflammation or autoimmune, or I&I, field that may result from the 2016 Agreement will also be subject to the exclusive options described above.

We will retain rights to any program that Celgene does not designate for further development or as to which it does not exercise its option.

Under the terms of the 2016 Agreement, following Celgene's exercise of its option with respect to a program, we or our affiliates and Celgene will enter into either a co-development and co-commercialization agreement if such program is in the IO field, or a license agreement if such program is in the I&I field. Under each co-development and co-commercialization agreement, the parties will co-develop and co-commercialize licensed products worldwide. Either we or Celgene will lead development and commercialization of licensed products for the United States and Celgene will lead development and commercialization of licensed products outside of the United States. Depending on the country, the parties will each have the right to provide a portion of field-based marketing activities. Under each license agreement, Celgene will have the sole right to develop and commercialize licensed products worldwide.

*Co-development and co-commercialization agreements.* Under each co-development and co-commercialization agreement entered into under the 2016 Agreement, the parties will split all post-option-exercise worldwide development costs, subject to specified exceptions, as well as any profits from any net sales of, or commercialization losses related to, licensed products. Celgene has the option to designate one program in the IO field as the 65/35 program, for which Celgene will be the lead party for the United States and will have a 65% profit or loss share. For programs in the IO field other than the 65/35 program, the parties will alternate, on a program-by-program basis, being the lead party for the United States, with us having the right to be the lead party for the first such program, and each will have a 50% profit or loss share. The lead party for the United States will book commercial sales of licensed products, if any, in the United States, and Celgene will book commercial sales of licensed products, if any, outside of the United States.

*License agreements.* Under each license agreement under the 2016 Agreement, Celgene will be responsible for all post-option-exercise worldwide development and associated costs, subject to specified exceptions, as well as worldwide commercialization and associated costs, for licensed products.

*Financial terms.* Under the terms of the 2016 Agreement, we received an initial upfront payment in the amount of \$200 million. The research term may be extended for up to two, or in specified cases, up to four, additional years by paying a \$40 million per-year extension fee. Celgene will pay an \$8 million designation fee for each program that Celgene designates for further development and for each continuation program. For each program as to which Celgene exercises its option to develop and commercialize, subject to antitrust clearance, Celgene will pay an option exercise fee of at least \$30 million for any designated development program and at least \$35 million for any continuation programs. In certain cases, Celgene may exercise its option to develop and commercialize two early-stage I&I programs, prior to Celgene designating the program for further development, by paying an option exercise fee of \$10 million.

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## [Table of Contents](#)

For the co-development and co-commercialization program Celgene designates the 65/35 program in the IO field, we are eligible to receive up to \$209 million in potential milestone-based payments. The potential milestone-based payments for that program are comprised of: (i) a \$25 million milestone-based payment upon achievement of a specified clinical development event and (ii) up to \$184 million in milestone-based payments upon achievement of specified regulatory milestone events. For each co-development and co-commercialization program in the IO field other than the 65/35 program, we are eligible to receive up to \$169 million in potential milestone-based payments. The potential milestone-based payments for such programs are comprised of: (i) a \$20 million milestone-based payment upon achievement of a specified clinical development event and (ii) up to \$149 million in milestone-based payments upon achievement of specified regulatory milestone events.

For each licensed program in the I&I field, we are eligible to receive royalties at tiered, low double-digit percentage rates on Celgene's net sales, if any, of the applicable licensed products and up to \$386 million in potential milestone-based payments. The potential milestone-based payments for such programs are comprised of: (i) a \$25 million milestone-based payment upon achievement of a specified clinical development event, (ii) up to \$236 million in milestone-based payments upon achievement of specified regulatory milestone events, and (iii) up to \$125 million in milestone-based payments upon achievement of specified commercial milestone events.

*Opt-out right.* Under the 2016 Agreement, the Company may elect to opt out of the cost and profit share under any co-development and co-commercialization agreement, subject to specified exceptions. Upon opting out, Celgene will have the sole right to develop, manufacture and commercialize the applicable licensed products throughout the world, at its cost, and we will undertake transitional activities reasonably necessary to transfer the development, manufacture and commercialization of such licensed products to Celgene, at our expense. Further, in lieu of the profit or loss sharing described above, we would be eligible to receive royalties at tiered, low double-digit percentage rates on Celgene's net sales, if any, of the applicable licensed products. However, we would continue to be eligible to receive the developmental and regulatory milestone-based payments described above.

*Term.* The term of the 2016 Agreement commenced on May 17, 2016 and, if not terminated earlier, will expire upon the later of the last-to-expire of the research term and all option exercise periods, or, if an option is exercised by Celgene for one or more programs in the collaboration, upon the termination or expiration of the last-to-exist co-development and co-commercialization agreement or license agreement, as applicable, for any such program.

*Termination.* Subject to specified exceptions, Celgene may terminate the 2016 Agreement in its entirety for any reason by providing us with prior written notice if there are no active co-development and co-commercialization agreements or license agreements in place or on a program-by-program basis if there are no active co-development and co-commercialization agreements or license agreements in place for the terminated program(s). Either party may terminate the 2016 Agreement for the insolvency of the other party. On a program-by-program basis, prior to the exercise of an option, either party may terminate the 2016 Agreement either in its entirety or with respect to one or more programs on prior written notice to the other party in the case of an uncured material breach by the other party that frustrates the fundamental purpose of the 2016 Agreement. Following the exercise of an option for a program, either party may terminate the 2016 Agreement with respect to such program if such party terminates the co-development and co-commercialization agreement or license agreement for such program for an uncured material breach by the other party that frustrates the fundamental purpose of such agreement. Either party may terminate a co-development and co-commercialization agreement or a license agreement upon the bankruptcy or insolvency of the other party. Either party also has the right to terminate the co-development and co-commercialization agreement or license agreement if the other party or any of its affiliates challenges the validity, scope or enforceability of or otherwise opposes, any patent included within the intellectual property rights licensed to the other party under such agreement.

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## [Table of Contents](#)

*Exclusivity.* While any of Celgene's options remain available under the 2016 Agreement, subject to specified exceptions, we may not directly or indirectly develop, manufacture or commercialize, outside of the 2016 Agreement, any therapeutic modality in the IO field or the I&I field with specified activity against a metabolic target.

During the term of each co-development and co-commercialization agreement and license agreement, subject to specified exceptions, neither we nor Celgene may directly or indirectly develop, manufacture or commercialize outside of such agreement any therapeutic modality in any field with specified activity against the metabolic target that is the focus of the program licensed under such agreement.

### ***AG-120 Letter Agreement***

On May 17, 2016, we entered into a letter agreement with Celgene regarding ivosidenib (AG-120), or the AG-120 Letter Agreement. Under the AG-120 Letter Agreement, the parties have agreed to terminate the 2010 Agreement, effective as of August 15, 2016, as to the program directed to the IDH1 target, for which ivosidenib (AG-120) is the lead development candidate. Under the 2010 Agreement, Celgene had held development and commercialization rights to the IDH1 program outside of the United States, and we had held such rights inside the United States. As a result of the AG-120 Letter Agreement, we obtained global rights to ivosidenib (AG-120) and the IDH1 program. Neither party has any further financial obligation, including royalties or milestone payments, to the other concerning ivosidenib (AG-120) or the IDH1 program. Under the AG-120 Letter Agreement, the parties have also agreed to conduct specified transitional activities in connection with the termination. In addition, pursuant to the AG-120 Letter Agreement, the parties are released from their exclusivity obligations under the 2010 Agreement with respect to the IDH1 program. The AG-120 Letter Agreement does not affect the global collaboration pursuant to the AG-881 Agreements, which are directed to both the IDH1 target and the IDH2 target.

### ***AG-881 Agreements***

On April 27, 2015, we entered into a joint worldwide development and profit share collaboration and license agreement with Celgene and our wholly owned subsidiary, Agios International Sarl, which was organized in Switzerland in April 2015, and we entered into a collaboration and license agreement with Celgene's wholly owned subsidiary, Celgene International II Sarl, or, collectively, the AG-881 Agreements. The AG-881 Agreements establish a worldwide collaboration focused on the development and commercialization of AG-881 products. Under the terms of the AG-881 Agreements, we received initial upfront payments totaling \$10.0 million in May 2015 and are eligible to receive milestone-based payments described below. We will split all worldwide development costs with Celgene equally, subject to specified exceptions, as well as any profits from any net sales of, or commercialization losses related to, licensed AG-881 products. Celgene will book commercial sales of licenses AG-881 products, if any, on a worldwide basis.

*Financial terms.* We are eligible to receive up to \$70.0 million in potential milestone payments related to AG-881 under the AG-881 Agreements. The potential milestone payments are comprised of: (i) a \$15.0 million milestone payment for filing of first NDA in a major market and (ii) up to \$55.0 million in milestone payments upon achievement of specified regulatory milestone events. We may also receive royalties at tiered, low- to mid-teen percentage rates on net sales if Celgene elects to not participate in the development and commercialization of AG-881.

*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 oversees and coordinates the overall conduct of the collaboration. The joint development committee oversees and coordinates development (including manufacturing of clinical supply) of medicines containing AG-881. The joint commercialization committee will oversee the commercialization (including manufacturing of commercial supply) of medicines containing AG-881. The joint patent committee oversees the parties' patent rights under the collaboration. If there is not unanimity with respect to matters pertaining to the development of AG-881, then neither party shall have decision-making authority with respect to such matter and neither party may take action with respect to such matter unless and until it is resolved by mutual consent.

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## [Table of Contents](#)

*Commercialization.* Under the terms of the AG-881 Agreements, we will lead commercialization of licensed AG-881 products within the United States and Celgene will lead commercialization of licensed AG-881 products outside of the United States. Depending on the market, the parties will each have the right to provide a portion of field-based marketing activities.

*Opt-out right.* Under the AG-881 Agreements, we may elect to opt out of the cost and profit split of the collaboration at any time after April 27, 2016 by providing at least 12 months written notice to Celgene. If we opt out, Celgene will have the sole right to develop, manufacture and commercialize licensed AG-881 products throughout the world, at its cost, and we will undertake transitional activities reasonably necessary to transfer the development, manufacture and commercialization of licensed AG-881 products to Celgene, at our cost.

If we elect to opt-out of the AG-881 Agreements, then, in lieu of the profit or loss sharing described above, we would be eligible to receive royalties at tiered, low to mid-teen percentage rates on Celgene's net sales of licensed AG-881 products.

*Term.* The term of the AG-881 Agreements will continue, unless earlier terminated, as described below, as long as we and Celgene continue to develop or commercialize licensed AG-881 products, or, in the event we opt out of the AG-881 Agreements, until expiration of the royalty term for AG-881 products.

*Termination.* Celgene may terminate the AG-881 Agreements for convenience upon ninety days written notice to us. Either we or Celgene may terminate the AG-881 Agreements if the other party is in material breach and fails to cure such breach within the specified cure period. Either we or Celgene may terminate the AG-881 Agreements in the event of specified insolvency events involving the other party. If one of the AG-881 Agreements terminates, the other will terminate automatically.

*Exclusivity.* Until termination or expiration of the AG-881 Agreements, neither we nor Celgene may directly or indirectly develop, manufacture or commercialize, outside of the AG-881 Agreements or the 2010 Agreement, any therapeutic modality with specified activity against both IDH1 and IDH2.

### **2010 Agreement and amendments**

In April 2010, we entered into the 2010 Agreement. The 2010 Agreement was amended in October 2011 and July 2014. The goal of the collaboration was to discover, develop and commercialize disease-altering therapies in oncology based on the Company's cancer metabolism research platform. We initially led discovery, preclinical and early clinical development for all cancer metabolism programs under the collaboration. The discovery phase of the collaboration under the 2010 Agreement expired in April 2016.

*Collaboration governance.* Upon agreement to terminate the 2010 Agreement, effective as of August 15, 2016, as to the program directed to the IDH1 target, for which ivosidenib (AG-120) is the lead development candidate, the sole program remaining under the 2010 Agreement is enasidenib, a co-commercialized licensed program. Under the terms of the 2010 Agreement, Celgene funds global development and commercialization of enasidenib. We have exercised our right to participate in a portion of commercialization activities in the United States for enasidenib in accordance with the applicable commercialization plan. The development and commercialization of enasidenib is managed by a set of joint committees comprised of equal numbers of representatives from each party. The joint steering committee oversees and coordinates the overall conduct of the collaboration. The joint development committee oversees and coordinates development (including manufacturing of clinical supply) of enasidenib. The joint commercialization committee will oversee the commercialization (including manufacturing of commercial supply) of the program.

*Diligence.* Each party must use commercially reasonable efforts to perform all activities for which such party is responsible under the collaboration.

*Exclusivity.* 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,

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## [Table of Contents](#)

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.

*Financial terms.* Under the 2010 Agreement, we are eligible to receive up to \$120.0 million in potential milestone payments payable for the enasidenib program. 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, which was earned in January 2016 in connection with the initiation of the IDHENTIFY clinical trial, (ii) up to \$70.0 million in milestone payments upon achievement of specified ex-U.S. regulatory milestone events, and (iii) a \$25.0 million milestone payment upon achievement of a specified commercial milestone event.

We are eligible to receive royalties at tiered, low- to mid-teen percentage rates on net sales and we have the option to participate in the development and commercialization of certain products in the United States. Assuming all other revenue recognition criteria are met, royalty payments will be recognized as revenue in the period in which they are earned.

*Termination.* Celgene may terminate the 2010 Agreement for convenience in its entirety or with respect to enasidenib upon ninety days written notice to us. Either we or Celgene may terminate the 2010 Agreement, in its entirety or with respect to enasidenib, if the other party is in material breach and fails to cure such breach within the specified cure period. Either we or Celgene may terminate the 2010 Agreement in the event of specified insolvency events involving the other party.

If Celgene terminates the 2010 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; and royalties to which we may be entitled may be reduced or eliminated.

If Celgene terminates the 2010 Agreement for convenience or if we terminate the agreement as a result of Celgene's uncured material breach, the license we granted to Celgene with respect to enasidenib 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 the enasidenib 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 enasidenib, ivosidenib (AG-120), AG-881 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, 2016, we had a portfolio of issued and pending U.S. and foreign patent applications. A significant portion of our issued and pending patent applications pertain to our key development programs, including enasidenib, ivosidenib (AG-120), AG-881 and AG-348. We currently own issued patents in the United States covering for enasidenib, ivosidenib (AG-120), AG-881 and AG-348 as compositions of matter.

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## [Table of Contents](#)

In addition to the pending patent applications and issued patents 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,

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## [Table of Contents](#)

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, MIO and RGDs. There are other companies working to develop therapies in the fields of cancer metabolism, MIO and RGDs. These companies include divisions of large pharmaceutical companies and biotechnology companies of various sizes.

*Cancer.* In the field of cancer metabolism, our principal competitors include AstraZeneca Plc.; Bayer AG; Calithera Biosciences; Cornerstone Pharmaceuticals, Inc.; Daiichi Sankyo Company, Ltd.; Eli Lilly and Company; Forma Therapeutics Holdings, LLC, or Forma; GlaxoSmithKline plc; Merck & Co.; Novartis International AG, or Novartis; Pfizer, Inc.; and Roche Holdings, Inc. and its subsidiary Genentech, Inc. For example, Novartis and Forma are conducting phase 1 clinical trials of their IDH1 mutant inhibitors, IDH305 and FT-2102, respectively, in patients with advanced malignancies including AML and MDS. 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 immunology 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. In the MIO field, our principal competitors include AstraZeneca PLC, Merck, Genentech, Bristol-Myers Squibb Company and Novartis.

*Rare genetic metabolic disorders.* In the field of RGDs, our principal competitors include Alexion Pharmaceuticals, Inc.; BioMarin Pharmaceutical, Inc.; Genzyme Corporation, 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

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## [Table of Contents](#)

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 enasidenib, ivosidenib (AG-120), AG-881 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 yet 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 NDA to the FDA.

Enasidenib, ivosidenib (AG-120), AG-881 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 and sale of any companion diagnostics we develop.

### **Research and Development Expenses**

For the years ended December 31, 2016, 2015 and 2014, company-sponsored research and development expenses were \$220.2 million, \$141.8 million and \$100.4 million, respectively.

### **Review and Approval of Drugs in the United States**

In the United States, the FDA approves and regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. The failure to comply with requirements under the FDCA and other

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## [Table of Contents](#)

applicable laws at any time during the product development process, approval process or after approval may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of 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 investigations and penalties brought by the FDA and the Department of Justice or other governmental entities.

Our product candidates must be approved by the FDA through the NDA. An applicant seeking approval to market and distribute a new drug product in the United States must typically undertake 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 take effect before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical 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 product for each indication;
- preparation and submission to the FDA of a NDA requesting marketing for one or more proposed indications;
- review by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are 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 product's identity, strength, quality and purity;
- satisfactory completion of FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data;
- payment of user fees and securing FDA approval of the NDA; and
- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and the potential requirement to conduct post-approval studies.

### ***Preclinical studies***

Before an applicant begins testing a compound with potential therapeutic value in humans, the drug candidate enters the preclinical testing stage. Preclinical studies include laboratory evaluation of product chemistry, toxicity and formulation, and the purity and stability of the drug substance, as well as *in vitro* and animal studies to assess the potential safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. The results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, are submitted 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.

Applicants usually must complete some long-term nonclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, and must also develop additional information about the chemistry and physical characteristics of the drug and finalize a process for manufacturing the drug in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing

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## [Table of Contents](#)

quality batches of the drug candidate and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final drug product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

### ***Human clinical trials in support of an NDA***

Clinical trials involve the administration of the investigational product 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 inclusion and exclusion criteria, 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. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to a proposed clinical trial 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. Following commencement of a clinical trial under an IND, the FDA may place a clinical hold on that trial. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a specific protocol or part of a protocol is not allowed to proceed, while other protocols may do so. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical hold or partial clinical hold, an investigation may only resume after the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed.

In addition, an IRB representing 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 a continuing review and reapprove the study at least annually. 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 on their [ClinicalTrials.gov](http://ClinicalTrials.gov) website.

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

- Phase 1.*** The drug is initially introduced into a small number of healthy human subjects or, in certain indications such as cancer, patients with the target disease or condition (e.g., cancer) and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness and to determine optimal dosage.
- 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.*** These clinical trials are commonly referred to as “pivotal” studies, which denotes a study which presents the data that the FDA or other relevant regulatory agency will use to determine whether or not to approve a drug. The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate 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.
- Phase 4.*** Post-approval studies may be conducted after initial marketing approval. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication.

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## [Table of Contents](#)

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. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the drug; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The FDA or the sponsor or the data monitoring committee 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, or an institution it represents, 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. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted.

A sponsor may choose, but is not required, to conduct a foreign clinical study under an IND. When a foreign clinical study is conducted under an IND, all FDA IND requirements must be met unless waived. When the foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with FDA certain regulatory requirements in order to use the study as support for an IND or application for marketing approval. Specifically, on April 28, 2008, the FDA amended its regulations governing the acceptance of foreign clinical studies not conducted under an investigational new drug application as support for an IND or a new drug application. The final rule provides that such studies must be conducted in accordance with GCP, including review and approval by an independent ethics committee, or IEC, and informed consent from subjects. The GCP requirements in the final rule encompass both ethical and data integrity standards for clinical studies. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical studies, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign studies are conducted in a manner comparable to that required for IND studies.

Concurrent with clinical trials, companies often complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and, among other things, must develop methods for testing the identity, strength, quality, purity, and potency of the final drug. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

### ***Review of an NDA by the FDA***

Assuming successful completion of required clinical testing and other requirements, the results of the preclinical studies and clinical trials, 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 drug product for one or more indications. Under federal law, the submission of most NDAs is additionally subject to an 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 \$114,000 per product and \$585,000 per establishment. These fees are typically increased annually. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for drugs with orphan designation and a waiver for certain small businesses, an exception from the establishment fee when the establishment does not engage in manufacturing the drug during a particular fiscal year, and an exception from the product fee for a drug that is the same as another drug approved under an abbreviated pathway.

The FDA conducts a preliminary review of an NDA generally within 60 calendar days of its receipt and strives to inform the sponsor by the 74th day after the FDA's receipt of the submission to determine whether the application is 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

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## [Table of Contents](#)

submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. Under that agreement, 90% of applications seeking approval of New Molecular Entities, or NMEs, are meant to be reviewed within ten months from the date on which FDA accepts the NDA for filing, and 90% of applications for NMEs that have been designated for “priority review” are meant to be reviewed within six months of the filing date. For applications seeking approval of drugs that are not NMEs, the ten-month and six-month review periods run from the date that FDA receives the application. The review process and the Prescription Drug User Fee Act goal date may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA submission, including drug component manufacturing (e.g., active pharmaceutical ingredients), finished drug product manufacturing, and control testing laboratories. 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. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP.

In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events, and whether the product is a new molecular entity. REMS can include medication guides, physician communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU may include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The FDA may require a REMS before approval or post-approval if it becomes aware of a serious risk associated with use of the product. The requirement for a REMS can materially affect the potential market and profitability of a product.

The FDA is required to refer an application for a novel drug to an advisory committee or explain why such referral was not made. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

### ***Fast track, breakthrough therapy and priority review designations***

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs are fast track designation, breakthrough therapy designation and priority review designation.

First, the FDA may designate a product for fast track review if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For fast track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a fast track product’s application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a fast track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay 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 application 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.

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## [Table of Contents](#)

Second, in 2012, Congress enacted the Food and Drug Administration Safety and Innovation Act, or FDASIA. This law established a new regulatory scheme allowing for expedited review of products designated as “breakthrough therapies.” A product may be designated as a breakthrough therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to breakthrough therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving more senior staff in the review process; assigning a cross-disciplinary project lead for the review team; and taking other steps to design the clinical trials in an efficient manner.

Third, the FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting product reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and evidence of safety and effectiveness in a new subpopulation. A priority designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA’s goal for taking action on a marketing application from ten months to six months.

Under Section 524 of the FDCA, the FDA is authorized to award a priority review voucher to sponsors of certain tropical disease product applications that meet the criteria specified in the Act. A priority review voucher may be used by the sponsor who obtains it or it may be transferred to another sponsor who may use it to obtain priority review for a different application. Priority review vouchers can result in the acceleration of review and approval of a product candidate by up to four months; the sponsor using the voucher must pay an extra user fee to support the review of the application, however. That fee is not subject to waivers, exemptions or reductions. In order to be eligible for a tropical disease priority review voucher, the application must be: for a listed tropical disease; submitted under Section 505(b)(1) of the FDCA or Section 351 of the Public Health Service Act after September 27, 2007; for a product that contains no active ingredient that has been approved in any other application under those statutory provisions; and must qualify for priority review. The FDA has identified in guidance those product applications for the prevention or treatment of tropical diseases that may qualify for a priority review voucher.

### *Accelerated approval pathway*

The FDA may grant accelerated approval to a product for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. Products granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a product, such as an effect on IMM. The FDA has limited

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## [Table of Contents](#)

experience with accelerated approvals based on intermediate clinical endpoints, but has indicated that such endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a product.

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a product, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the development and approval of products for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit.

The accelerated approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the product's clinical benefit. As a result, 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 product from the market on an expedited basis. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

### ***The FDA's decision on an NDA***

On the basis of the FDA's evaluation of the NDA and accompanying information, including the results of the 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 product 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.

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 the 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 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, many 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.

### ***Post-approval requirements***

Drugs manufactured or distributed 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. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

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

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## [Table of Contents](#)

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 the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area 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 REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, suspension of the approval, or 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 NDAs or supplements to approved NDAs, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- 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.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, and its implementing regulations, as well as the Drug Supply Chain Security Act, or DSCA, which regulate the distribution and tracing of prescription drugs and prescription drug samples at the federal level, and set minimum standards for the regulation of drug distributors by the states. The PDMA, its implementing regulations and state laws limit the distribution of prescription pharmaceutical product samples, and the DSCA imposes requirements to ensure accountability in distribution and to identify and remove counterfeit and other illegitimate products from the market.

### ***Abbreviated new drug applications for generic drugs***

In 1984, with passage of the Hatch-Waxman Amendments to the FDCA, Congress established an abbreviated regulatory scheme authorizing the FDA to approve generic drugs that are shown to contain the same active ingredients as, and to be bioequivalent to, drugs previously approved by the FDA pursuant to NDAs. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the agency. An ANDA is a comprehensive submission that contains, among other things, data and information pertaining to the active pharmaceutical ingredient, bioequivalence, drug product formulation, specifications and stability of the generic drug, as well as analytical methods, manufacturing process validation data and quality control procedures. ANDAs are “abbreviated” because they generally do not include preclinical and clinical data to demonstrate safety and effectiveness. Instead, in support of such applications, a generic manufacturer may rely on the preclinical and clinical testing previously conducted for a drug product previously approved under an NDA, known as the reference-listed drug, or RLD.

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## [Table of Contents](#)

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, the strength of the drug and the conditions of use of the drug. At the same time, the FDA must also determine that the generic drug is “bioequivalent” to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if “the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug.”

Upon approval of an ANDA, the FDA indicates whether the generic product is “therapeutically equivalent” to the RLD in its publication “Approved Drug Products with Therapeutic Equivalence Evaluations,” also referred to as the “Orange Book.” Physicians and pharmacists consider a therapeutic equivalent generic drug to be fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA’s designation of therapeutic equivalence often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

Under the Hatch-Waxman Amendments, the FDA may not approve an ANDA until any applicable period of non-patent exclusivity for the RLD has expired. The FDCA provides a period of five years of non-patent data exclusivity for a new drug containing a new chemical entity. For the purposes of this provision, a new chemical entity, or NCE, is a drug that contains no active moiety that has previously been approved by the FDA in any other NDA. An active moiety is the molecule or ion responsible for the physiological or pharmacological action of the drug substance. In cases where such NCE exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification, in which case the applicant may submit its application four years following the original product approval.

The FDCA also provides for a period of three years of exclusivity if the NDA includes reports of one or more new clinical investigations, other than bioavailability or bioequivalence studies, that were conducted by or for the applicant and are essential to the approval of the application. This three-year exclusivity period often protects changes to a previously approved drug product, such as a new dosage form, route of administration, combination or indication. Three-year exclusivity would be available for a drug product that contains a previously approved active moiety, provided the statutory requirement for a new clinical investigation is satisfied. Unlike five-year NCE exclusivity, an award of three-year exclusivity does not block the FDA from accepting ANDAs seeking approval for generic versions of the drug as of the date of approval of the original drug product. The FDA typically makes decisions about awards of data exclusivity shortly before a product is approved.

### ***505(b)(2) NDAs***

As an alternative path to FDA approval for modifications to formulations or uses of products previously approved by the FDA pursuant to an NDA, an applicant may submit an NDA under Section 505(b)(2) of the FDCA. Section 505(b)(2) was enacted as part of the Hatch-Waxman Amendments and permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by, or for, the applicant. If the 505(b)(2) applicant can establish that reliance on FDA’s previous findings of safety and effectiveness is scientifically and legally appropriate, it may eliminate the need to conduct certain preclinical or clinical studies of the new product. The FDA may also require companies to perform additional studies or measurements, including clinical trials, to support the change from the previously approved reference drug. The FDA may then approve the new product candidate for all, or some, of the label indications for which the reference drug has been approved, as well as for any new indication sought by the 505(b)(2) applicant.

### ***Hatch-Waxman patent certification and the 30-month stay***

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant’s product or an approved method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA or 505(b)(2) applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the

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## [Table of Contents](#)

reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. Specifically, the applicant must certify with respect to each patent that:

- the required patent information has not been filed;
- the listed patent has expired;
- the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or
- the listed patent is invalid, unenforceable or will not be infringed by the new product.

A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid or unenforceable is called a Paragraph IV certification. If the applicant does not challenge the listed patents or indicates that it is not seeking approval of a patented method of use, the application will not be approved until all the listed patents claiming the referenced product have expired (other than method of use patents involving indications for which the applicant is not seeking approval).

If the ANDA or 505(b)(2) applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA or the 505(b)(2) application has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA or 505(b)(2) application until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the applicant. The ANDA or 505(b)(2) application also will not be approved until any applicable non-patent exclusivity listed in the Orange Book for the branded reference drug has expired.

### ***Pediatric studies and exclusivity***

Under the Pediatric Research Equity Act, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the drug product 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. With enactment of FDASIA 2012, sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests, and any other information required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other, and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

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. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in FDASIA. Unless and until FDA promulgates a regulation stating otherwise, the pediatric data requirements do not apply to products with orphan designation.

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent and orphan exclusivity. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months.

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## [Table of Contents](#)

This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application. With regard to patents, the six-month pediatric exclusivity period will not attach to any patents for which an ANDA or 505(b)(2) applicant submitted a paragraph IV patent certification, unless the NDA sponsor or patent owner first obtains a court determination that the patent is valid and infringed by the proposed product.

### ***Orphan drug designation and exclusivity***

Under the Orphan Drug Act, the FDA may designate a drug product as an “orphan drug” if it is intended to treat a rare disease or condition, generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for treatment of the disease or condition will be recovered from sales of the product. A company must request orphan drug designation before submitting an NDA for the drug and rare disease or condition. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan drug designation does not shorten the PDUFA goal dates for the regulatory review and approval process, although it does convey certain advantages such as tax benefits and exemption from the PDUFA application fee.

If a product with orphan designation receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the product generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor’s marketing application for the same drug for the same indication for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different drug for the same rare disease or condition, nor does it block the approval of the same drug for different indications. If a drug designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity. Orphan exclusivity will not bar approval of another product under certain circumstances, including if a subsequent product with the same drug for the same indication is shown to be clinically superior to the approved product on the basis of greater efficacy or safety, or providing a major contribution to patient care, or if the company with orphan drug exclusivity is not able to meet market demand.

### ***Patent term restoration and extension***

A patent claiming a new drug product or its method of use may be eligible for a limited patent term extension, also known as patent term restoration, under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. Patent term extension is generally available only for drug products whose active ingredient has not previously been approved by the FDA. The restoration period granted is typically one-half the time between the effective date of an IND and the submission date of an NDA, plus the time between the submission date of an NDA and the ultimate approval date. Patent term extension cannot be used to extend the remaining term of a patent past a total of 14 years from the product’s approval date. Only one patent applicable to an approved drug product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple drugs for which approval is sought can only be extended in connection with one of the approvals. The United States PTO reviews and approves the application for any patent term extension in consultation with the FDA.

### ***FDA approval and regulation of companion diagnostics***

If safe and effective use of a therapeutic depends on an *in vitro* diagnostic, then the FDA generally will require approval or clearance of that diagnostic, known as a companion diagnostic, at the same time that the FDA approves the therapeutic product. In August 2014, the FDA issued final guidance clarifying the requirements that will apply to approval of therapeutic products and *in vitro* companion diagnostics. According to the guidance, for novel drugs, a companion diagnostic device and its corresponding therapeutic should be approved or cleared contemporaneously by the FDA for the use indicated in the therapeutic product’s labeling.

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## [Table of Contents](#)

If FDA determines that a companion diagnostic device is essential to the safe and effective use of a novel therapeutic product or indication, FDA generally will not approve the therapeutic product or new therapeutic product indication if the companion diagnostic device is not approved or cleared for that indication. Approval or clearance of the companion diagnostic device will ensure that the device has been adequately evaluated and has adequate performance characteristics in the intended population. The review of *in vitro* companion diagnostics in conjunction with the review of our therapeutic treatments for cancer will, therefore, likely involve coordination of review by the FDA's Center for Drug Evaluation and Research and the FDA's Center for Devices and Radiological Health Office of In Vitro Diagnostics Device Evaluation and Safety.

Under the FDCA, *in vitro* diagnostics, including companion diagnostics, are regulated as medical devices. In the United States, the FDCA and its implementing regulations, and other federal and state statutes and regulations govern, among other things, medical device design and development, preclinical and clinical testing, premarket clearance or approval, registration and listing, manufacturing, labeling, storage, advertising and promotion, sales and distribution, export and import, and post-market surveillance. Unless an exemption applies, diagnostic tests require marketing clearance or approval from the FDA prior to commercial distribution. The two primary types of FDA marketing authorization applicable to a medical device are premarket notification, also called 510(k) clearance, and premarket approval, or PMA approval.

The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, can take several years or longer. It involves a rigorous premarket review during which the applicant must prepare and provide the FDA with reasonable assurance of the device's safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications are subject to an application fee, which exceeds \$250,000 for most PMAs. In addition, PMAs for certain devices must generally include the results from extensive preclinical and adequate and well-controlled clinical trials to establish the safety and effectiveness of the device for each indication for which FDA approval is sought. In particular, for a diagnostic, a PMA application typically requires data regarding analytical and clinical validation studies. As part of the PMA review, the FDA will typically inspect the manufacturer's facilities for compliance with the Quality System Regulation, or QSR, which imposes elaborate testing, control, documentation and other quality assurance requirements.

PMA approval is not guaranteed, and the FDA may ultimately respond to a PMA submission with a not approvable determination based on deficiencies in the application and require additional clinical trial or other data that may be expensive and time-consuming to generate and that can substantially delay approval. 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's evaluation of the PMA or manufacturing facilities is not favorable, the FDA will deny approval of the PMA or issue a not approvable letter. A not approvable letter will outline the deficiencies in the application and, where practical, will identify what is necessary to make the PMA approvable. The FDA may also determine that additional clinical trials are necessary, in which case the PMA approval may be delayed for several months or years while the trials are conducted and then the data submitted in an amendment to 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 applicant. 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. Once granted, PMA approval may be withdrawn by the FDA if compliance with post approval requirements, conditions of approval or other regulatory standards are not maintained or problems are identified following initial marketing.

After a device is placed on the market, it remains subject to significant regulatory requirements. Medical devices may be marketed only for the uses and indications for which they are cleared or approved. Device manufacturers must also establish registration and device listings with the FDA. A medical device manufacturer's manufacturing processes and those of its suppliers are required to comply with the applicable portions of the

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## [Table of Contents](#)

QSR, which cover the methods and documentation of the design, testing, production, processes, controls, quality assurance, labeling, packaging and shipping of medical devices. Domestic facility records and manufacturing processes are subject to periodic unscheduled inspections by the FDA. The FDA also may inspect foreign facilities that export products to the United States.

### **Review and Approval of Drugs in Europe and other Foreign Jurisdictions**

In addition to regulations in the United States, a manufacturer is subject to a variety of regulations in foreign jurisdictions to the extent they choose to sell any drug products in those foreign countries. Even if a manufacturer obtains FDA approval of a product, it must still obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. To obtain regulatory approval of an investigational drug or biological product in the European Union, a manufacturer must submit a marketing authorization application to the European Medicines Agency or EMA. For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, clinical trials are to be conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

#### ***Clinical trial approval in the European Union***

Pursuant to the currently applicable Clinical Trials Directive 2001/20/EC and the Directive 2005/28/EC on Good Clinical Practice, an applicant must obtain the approval from the competent national authority of the EU Member State in which the clinical trial is to be conducted. If the clinical trial is conducted in different EU Member States, the competent authorities in each of these EU Member States must provide their approval for the conduct of the clinical trial. Furthermore, the applicant may only start a clinical trial at a specific study site after the competent ethics committee has issued a favorable opinion.

In April 2014, the European Union adopted a new Clinical Trials Regulation (EU) No 536/2014, which is set to replace the current Clinical Trials Directive 2001/20/EC. The new Clinical Trials Regulation will be directly applicable in and binding in all 28 EU Member States without the need for any national implementing legislation. The new Clinical Trials Regulation (EU) No 536/2014 will become applicable no earlier than 28 May 2016. It will overhaul the current system of approvals for clinical trials in the European Union. Specifically, the new legislation aims at simplifying and streamlining the approval of clinical trials in the EU. Under the new coordinated procedure for the approval of clinical trials, the sponsor of a clinical trial will be required to submit a single application for approval of a clinical trial to a reporting EU Member State (RMS) through an EU Portal. The submission procedure will be the same irrespective of whether the clinical trial is to be conducted in a single EU Member State or in more than one EU Member State. The Clinical Trials Regulation also aims to streamline and simplify the rules on safety reporting for clinical trials.

#### ***Marketing authorization***

In the European Union, marketing authorizations for medicinal products can be obtained through several different procedures founded on the same basic regulatory process.

The centralized procedure provides for the grant of a single marketing authorization that is valid for all EU Member States. The centralized procedure is compulsory for medicinal products produced by certain biotechnological processes, products designated as orphan medicinal products, and products with a new active substance indicated for the treatment of certain diseases. It is optional for those products that are highly innovative or for which a centralized process is in the interest of patients. Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of a marketing authorization application is 210 days, excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the Committee for Medicinal Products for Human use or CHMP. Accelerated evaluation may be granted by the CHMP in exceptional cases. These are defined as circumstances in which a

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## [Table of Contents](#)

medicinal product is expected to be of a “major public health interest.” Three cumulative criteria must be fulfilled in such circumstances: the seriousness of the disease, such as heavy disabling or life-threatening diseases, to be treated; the absence or insufficiency of an appropriate alternative therapeutic approach; and anticipation of high therapeutic benefit. In these circumstances, the EMA ensures that the opinion of the CHMP is given within 150 days.

The decentralized procedure provides for approval by one or more other concerned EU Member States of an assessment of an application for marketing authorization conducted by one EU Member State, known as the reference EU Member State. In accordance with this procedure, an applicant submits an application for marketing authorization to the reference EU Member State and the concerned EU Member States. This application is identical to the application that would be submitted to the EMA for authorization through the centralized procedure. The reference EU Member State prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. The resulting assessment report is submitted to the concerned EU Member States who, within 90 days of receipt must decide whether to approve the assessment report and related materials. If a concerned EU Member State cannot approve the assessment report and related materials due to concerns relating to a potential serious risk to public health, disputed elements may be referred to the European Commission, whose decision is binding on all EU Member States. In accordance with the mutual recognition procedure, the sponsor applies for national marketing authorization in one EU Member State. Upon receipt of this authorization the sponsor can then seek the recognition of this authorization by other EU Member States. Authorization in accordance with either of these procedures will result in authorization of the medicinal product only in the reference EU Member State and in the other concerned EU Member States.

A marketing authorization may be granted only to an applicant established in the European Union. Regulation No. 1901/2006 provides that prior to obtaining a marketing authorization in the European Union, an applicant must demonstrate compliance with all measures included in a Pediatric Investigation Plan, or PIP, approved by the Pediatric Committee of the EMA, covering all subsets of the pediatric population, unless the EMA has granted a product-specific waiver, class waiver, or a deferral for one or more of the measures included in the PIP. Regulatory Data Exclusivity in the European Union.

In the European Union, innovative medicinal products authorized in the European Union on the basis of a full marketing authorization application (as opposed to an application for marketing authorization that relies on data available in the marketing authorization dossier for another, previously approved, medicinal product) are entitled to eight years of data exclusivity. During this period, applicants for authorization of generics of these innovative products cannot rely on data contained in the marketing authorization dossier submitted for the innovative medicinal product. Innovative medicinal products are also entitled to ten years’ market exclusivity. During this ten year period no generic of this medicinal product can be placed on the EU market. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to authorization, is held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity so that the innovator gains the prescribed period of data exclusivity, another company may market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

### ***Periods of authorization and renewals in the European Union***

A marketing authorization is valid for five years, in principle, and it may be renewed after five years on the basis of a reevaluation of the risk-benefit balance by the EMA or by the competent authority of the relevant EU Member State. To that end, the marketing authorization holder must provide the EMA or the relevant competent authority of the EU Member State with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. Once renewed, the marketing authorization is valid for an

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## [Table of Contents](#)

unlimited period, unless the European Commission or the relevant competent authority of the EU Member State decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal period. Any marketing authorization that is not followed by the marketing of the medicinal product on the EU market (in the case of the centralized procedure) or on the market of the EU Member State which delivered the marketing authorization within three years after authorization ceases to be valid.

### ***Regulatory requirements after marketing authorization***

Similarly to the United States, both marketing authorization holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA and the competent authorities of the individual EU Member States both before and after grant of the manufacturing and marketing authorizations.

The holder of an EU marketing authorization for a medicinal product must also comply with EU pharmacovigilance legislation and its related regulations and guidelines which entail many requirements for conducting pharmacovigilance, or the assessment and monitoring of the safety of medicinal products. These rules can impose on central marketing authorization holders for medicinal products the obligation to conduct a labor intensive collection of data regarding the risks and benefits of marketed products and to engage in ongoing assessments of those risks and benefits, including the possible requirement to conduct additional clinical studies.

The manufacturing process for medicinal products in the European Union is highly regulated and regulators may shut down manufacturing facilities that they believe do not comply with regulations. Manufacturing requires a manufacturing authorization, and the manufacturing authorization holder must comply with various requirements set out in the applicable EU laws, regulations and guidance, including Directive 2001/83/EC, Directive 2003/94/EC, Regulation (EC) No 726/2004 and the European Commission Guidelines for Good Manufacturing Practice. These requirements include compliance with EU cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients, including the manufacture of active pharmaceutical ingredients outside of the European Union with the intention to import the active pharmaceutical ingredients into the European Union. Similarly, the distribution of medicinal products into and within the European Union is subject to compliance with the applicable EU laws, regulations and guidelines, including the requirement to hold appropriate authorizations for distribution granted by the competent authorities of the EU Member States.

In the European Union, the advertising and promotion of our products are subject to EU Member States' laws governing promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. In addition, other legislation adopted by individual EU Member States may apply to the advertising and promotion of medicinal products. These laws require that promotional materials and advertising in relation to medicinal products comply with the product's Summary of Product Characteristics, or SmPC, as approved by the competent authorities. Promotion of a medicinal product that does not comply with the SmPC is considered to constitute off-label promotion. The off-label promotion of medicinal products is prohibited in the European Union. The applicable laws at the EU level and in the individual EU Member States also prohibit the direct-to-consumer advertising of prescription-only medicinal products. These laws may further limit or restrict the advertising and promotion of our products to the general public and may also impose limitations on our promotional activities with health care professionals.

### ***Orphan drug designation and exclusivity in the European Union***

Regulation (EC) No 141/2000 and Regulation (EC) No. 847/2000 provide that a product can be designated as an orphan medicinal product by the European Commission if its sponsor can establish: that the product is intended for the diagnosis, prevention or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the European Union when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the European Union and that without incentives the medicinal product is unlikely to be developed. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the European Union or, if such method exists, the medicinal product will be

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## [Table of Contents](#)

of significant benefit to those affected by that condition. Once authorized, orphan medicinal products are entitled to ten years of market exclusivity in all EU Member States and in addition a range of other benefits during the development and regulatory review process including scientific assistance for study protocols, authorization through the centralized marketing authorization procedure covering all member countries and a reduction or elimination of registration and marketing authorization fees. However, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the ten year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if this product is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if it can be demonstrated on the basis of available evidence that the original orphan medicinal product is sufficiently profitable not to justify maintenance of market exclusivity.

### **Pharmaceutical Coverage, Pricing and Reimbursement**

In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Patients are unlikely to use our products unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our products. Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Even if our product candidate is approved, sales of our products will depend, in part, on the extent to which third-party payors, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage, and establish adequate reimbursement levels for, such products. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company 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 marketing approvals. Nonetheless, product candidates may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover our product candidate could reduce physician utilization of our products once approved and have a material adverse effect on our sales, results of operations and financial condition. Additionally, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a drug product does not assure that other payors will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor. Third-party reimbursement and coverage may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

The containment of healthcare costs also has become a priority of federal, state and foreign governments and the prices of drugs have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit a company's revenue generated from the sale of any approved products. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive marketing approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

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## [Table of Contents](#)

Outside the United States, ensuring adequate coverage and payment for our product candidate will face challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory marketing approval for a product and may require us to conduct a clinical trial that compares the cost effectiveness of our product candidate or products to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in our commercialization efforts.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that 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 drug candidate to currently available therapies or so called health technology assessments, in order to obtain reimbursement or pricing approval. For example, the European Union provides options for its member states to restrict the range of 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 product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other member states allow companies to fix their own prices for products, but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the European Union have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage healthcare expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the European Union. The downward pressure on health care costs in general, particularly prescription drugs, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various European Union member states, and parallel trade, i.e., arbitrage between low-priced and high-priced member states, can further reduce prices. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products, if approved in those countries.

### **Healthcare Law and Regulation**

Healthcare providers and third-party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with providers, consultants, third-party payors and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, reporting of payments to physicians and teaching physicians and patient privacy laws and regulations and other healthcare laws and regulations that may constrain our business and/or financial arrangements. Restrictions under applicable federal and state healthcare laws and regulations, include the following:

- the United States federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, paying, 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, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;
- the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious or fraudulent or knowingly making, using or causing to be made or used a false record or 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, or HIPAA, which created additional federal criminal laws that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;

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## [Table of Contents](#)

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose 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 known as the federal Physician Payments Sunshine Act, under the Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act, or the Affordable Care Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the United States Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to healthcare items or services that are reimbursed by non-governmental third-party payors, including private insurers.

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. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

### **Healthcare Reform**

A primary trend in the United States healthcare industry and elsewhere is cost containment. There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and other medical products, government control and other changes to the healthcare system in the United States.

By way of example, the United States and state governments continue to propose and pass legislation designed to reduce the cost of healthcare. In March 2010, the United States Congress enacted the Affordable Care Act, which, among other things, includes changes to the coverage and payment for products under government health care programs. Among the provisions of the Affordable Care Act of importance to our potential drug candidates are:

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, although this fee would not apply to sales of certain products approved exclusively for orphan indications;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of "average manufacturer price," or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices and extending rebate liability to prescriptions for individuals enrolled in Medicare Advantage plans;

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## [Table of Contents](#)

- addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;
- expanded the types of entities eligible for the 340B drug discount program;
- established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 50% point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- the Independent Payment Advisory Board, or IPAB, which has authority to recommend certain changes to the Medicare program to reduce expenditures by the program that could result in reduced payments for prescription drugs. However, the IPAB implementation has been not been clearly defined. PPACA provided that under certain circumstances, IPAB recommendations will become law unless Congress enacts legislation that will achieve the same or greater Medicare cost savings; and
- established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending. Funding has been allocated to support the mission of the Center for Medicare and Medicaid Innovation from 2011 to 2019.

Other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. For example, in August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.2 trillion for the years 2012 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2024 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. With the new Administration and Congress, there will likely be additional legislative changes, including potential repeal and replacement of certain provisions of the Affordable Care Act. It remains to be seen, however, precisely what the new legislation will provide, when it will be enacted and what impact it will have on the availability of healthcare and containing or lowering the cost of healthcare. Such reforms could have an adverse effect on anticipated revenue from product candidates that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop product candidates.

On December 13, 2016, President Obama signed the 21st Century Cures Act, or Cures Act, into law. The Cures Act is designed to modernize and personalize healthcare, spur innovation and research, and streamline the discovery and development of new therapies through increased federal funding of particular programs. It authorizes increasing funding for FDA to spend on innovation projects. The new law also amends the Public Health Service Act, or PHSA, to reauthorize and expand funding for the National Institutes of Health. The Act establishes the NIH Innovation Fund to pay for the cost of development and implementation of a strategic plan, early stage investigators and research. It also charges NIH with leading and coordinating expanded pediatric research. Further, the Cures Act directs the Centers for Disease Control and Prevention to expand surveillance of neurological diseases.

With amendments to the FDCA and the PHSA, Title III of the Cures Act seeks to accelerate the discovery, development, and delivery of new medicines and medical technologies. To that end, and among other provisions,

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## [Table of Contents](#)

the Cures Act reauthorizes the priority review voucher program for certain drugs intended to treat rare pediatric diseases; creates a new priority review voucher program for drug applications determined to be material threat medical countermeasure applications; revises the FDCA to streamline review of combination product applications; requires FDA to evaluate the potential use of “real world evidence” to help support approval of new indications for approved drugs; provides a new “limited population” approval pathway for antibiotic and antifungal drugs intended to treat serious or life-threatening infections; and authorizes FDA to designate a drug as a “regenerative advanced therapy,” thereby making it eligible for certain expedited review and approval designations.

### **Segment Reporting**

We are engaged solely in the discovery and development of medicines in the field of cellular metabolism. Accordingly, we have determined that we operate in one operating segment.

### **Our Scientific Founders and Advisors**

#### ***Founders***

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

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

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

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

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

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

- elucidating the role of the Bcl-2 family of oncogenes in regulating cell survival;

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## [Table of Contents](#)

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

### **Scientific Advisors**

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

<u>Name</u>	<u>Primary affiliation</u>
Craig B. Thompson, M.D.	Memorial Sloan-Kettering Cancer Center
Joan Brugge, Ph.D.	Harvard Medical School
Lewis C. Cantley, Ph.D.	The Cancer Center at Weill Cornell Medical College and New York-Presbyterian Hospital
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
Shin-San Michael Su, Ph.D.	Decibel Therapeutics
Marc Tessier-Lavigne, Ph.D.	Stanford University
Matthew Vander Heiden, M.D., Ph.D.	Koch Institute for Integrative Cancer Research at MIT

### **Employees**

As of December 31, 2016, we had 287 full-time employees, including 101 employees with M.D. or Ph.D. degrees. Of these full-time employees, 163 employees are engaged in research and development activities. None of our employees are 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 88 Sidney Street, Cambridge, Massachusetts 02139, and our telephone number is (617) 649-8600. Our website address is [www.agios.com](http://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](http://www.agios.com) as soon as reasonably practicable after they are filed with or furnished to the Securities and Exchange Commission, or SEC. These reports are also available at the SEC's website at [www.sec.gov](http://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.

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## [Table of Contents](#)

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](http://www.agios.com), under the heading “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., 88 Sidney Street, 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 1 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 \$198.5 million, \$117.7 million and \$53.5 million for the years ended December 31, 2016, 2015 and 2014, respectively. As of December 31, 2016, we had an accumulated deficit of \$483.2 million. We have never generated any revenue from product sales, have not completed the development of any product candidate and may never have a product candidate approved for commercialization. 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 agreements with Celgene Corporation and its subsidiaries, or Celgene, focused on cancer metabolism and metabolic immuno-oncology. We have devoted substantially all of our efforts to research and development. We are in clinical development stages 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, we 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:

- initiate and continue clinical trials for our product candidates, including our most advanced product candidates: enasidenib, ivosidenib (AG-120), AG-881 and AG-348;
- continue our research and preclinical development of our product candidates;
- seek to identify additional product candidates;
- seek marketing approvals for our product candidates that successfully complete clinical trials;
- establish a sales, marketing and distribution infrastructure to commercialize any medicines for which we may obtain marketing approval;
- require the manufacture of larger quantities of product candidates for clinical development and, potentially, commercialization;
- maintain, expand and protect our intellectual property portfolio;
- hire additional clinical, quality control and scientific personnel;
- add additional personnel to support our product development and planned future commercialization efforts and our operations;
- add equipment and physical infrastructure to support our research and development; and
- acquire or in-license other medicines and technologies.

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## [Table of Contents](#)

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 revenue that are significant or large enough to achieve profitability. We are currently in clinical testing stages for our most advanced 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 our 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. 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, 2016, together with anticipated interest income, and the anticipated expense reimbursements under our collaboration agreements will fund our operating and capital expenditure requirements through at least the end of 2018. Our estimate as to how long we expect our existing cash and cash equivalents to be available to fund our operations is based on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Further, changing circumstances, some of which may be beyond our control, could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional funds sooner than planned. 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, and developments regarding, our collaborations;
- 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. We do not expect to generate significant commercial revenue unless, and until, we obtain marketing approval for and commercialize at least one of our product candidates, which may not occur for many years, if at all. In addition, our product candidates, if approved, may not achieve commercial success. Even if we succeed in developing and commercializing one or more of our product candidates, we may never achieve sufficient sales revenue to achieve or maintain profitability. 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.

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## [Table of Contents](#)

### ***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 revenue, 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 collaborations, which are 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 require us to enter into agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. In addition, securing financing could require a substantial amount of time and attention from our management and may divert a disproportionate amount of their attention away from day-to-day activities, which may adversely affect our management's ability to oversee the development of our product candidates.

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.

### ***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, undertaking preclinical and clinical studies of our product candidates, and establishing a commercial infrastructure. All of our product candidates are still in preclinical and clinical development. We have not yet demonstrated our ability to successfully complete any large-scale or 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, assuming that it successfully completes all stages of research and development and achieves marketing approval, all of which is highly uncertain. 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.

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.

We expect our financial condition and operating results to continue to fluctuate significantly from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any quarterly or annual periods as indications of future operating performance.

### **Risks Related to the Discovery, Development, and Commercialization of our Product Candidates**

#### ***We do not know whether we will be able to develop any medicines of commercial value, based on our approach to the discovery and development of product candidates that target cellular metabolism.***

Our scientific approach focuses on using our proprietary technology to identify key metabolic enzymes in cancer, rare genetic metabolic disorders, or RGDs, or other diseased cells in the laboratory and then using these key enzymes to screen for and identify product candidates targeting cellular metabolism. In May 2016 we entered into a new collaboration agreement, or the 2016 Agreement, focused on metabolic immuno-oncology. Metabolic immuno-oncology is an emerging field of cancer research focused on altering the metabolic state of immune cells to enhance the body's immune response to cancer.

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## [Table of Contents](#)

Any medicines that we develop may not effectively correct metabolic pathways or alter the metabolic state of immune cells. 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, as well as in immune cells for the treatment of cancer. 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. In addition, our efforts in the emerging field of metabolic immuno-oncology may not be as successful as our efforts to date in cancer metabolism and RGDs. Furthermore, 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 revenue 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 which are still in 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, enasidenib, ivosidenib (AG-120) and AG-881 for the treatment of hematological and solid tumors and AG-348 for the treatment of PK deficiency. We or our collaborator have initiated clinical trials for these product candidates. We have not commenced clinical trials for any of our other product candidates. Our ability to generate product revenue will depend heavily on the successful development and eventual commercialization of these product candidates by our collaborators and us. The success of our product candidates will depend on many factors, including the following:

- successful enrollment in, and completion of, clinical trials;
- safety, tolerability and efficacy profiles that are satisfactory to the U.S. Food and Drug Administration, or FDA, or any comparable foreign regulatory authority for marketing approval;
- timely receipt of marketing approvals from applicable regulatory authorities;
- establishing both clinical and commercial manufacturing capabilities or making arrangements with third-party manufacturers;

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## [Table of Contents](#)

- the performance of our collaborators;
- 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.

Many of these factors are beyond our control, including clinical development, the regulatory submission process, potential threats to our intellectual property rights and the manufacturing, marketing and sales efforts of any collaborator. 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.***

We, and any collaborators, are not permitted to commercialize, market, promote or sell any product candidate in the United States without obtaining marketing approval from the FDA. Foreign regulatory authorities, such as the European Medicines Agency, or the EMA, impose similar requirements. We have not previously submitted a new drug application, or NDA, to the FDA or similar drug approval filings to comparable foreign regulatory authorities for any 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. Celgene submitted an NDA to the FDA for enasidenib in relapsed and/or refractory, or R/R, acute myeloid leukemia, or AML, in December 2016. We plan to explore a similar regulatory pathway for ivosidenib (AG-120), and we expect to submit a NDA ivosidenib (AG-120) in IDH1 mutant-positive R/R AML by the end of 2017. However, we can provide no assurance that we will successfully submit an NDA for ivosidenib (AG-120), or that such NDAs, once submitted, will receive regulatory approval on the timeframe we expect, or at all.

Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. The clinical development of our product candidates is susceptible to the risk of failure inherent at any stage of product development, including failure to demonstrate efficacy in a clinical trial or across a broad population of patients, the occurrence of adverse events that are severe or medically or commercially unacceptable, failure to comply with protocols or applicable regulatory requirements and determination by the FDA or any comparable foreign regulatory authority that a product candidate may not continue development or is not approvable. For instance, in December 2016, we withdrew our investigational new drug application for AG-519, our second PKR activator, following verbal notification of a clinical hold from the FDA relating to a previously disclosed case of drug-induced cholestatic hepatitis which occurred in our phase 1 clinical trial of AG-519 in healthy volunteers. Although these decisions and this hepatic adverse event finding do not affect our ongoing global phase 2 clinical trial (DRIVE PK) for AG-348, our first PKR activator, we cannot provide any assurances that there will not be similar or other treatment-related severe adverse events in DRIVE PK or our

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## [Table of Contents](#)

other clinical trials, that our other trials will not be placed on clinical hold in the future, or that patient recruitment for DRIVE PK or our other trials will not be adversely impacted.

It is possible that even if one or more of our product candidates has a beneficial effect, that effect will not be detected during clinical evaluation as a result of one or more of a variety of factors, including the size, duration, design, measurements, conduct or analysis of our clinical trials. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any. Similarly, in our clinical trials we may fail to detect toxicity of or intolerability caused by our product candidates, or mistakenly believe that our product candidates are toxic or not well tolerated when that is not in fact the case.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us, or any future collaborators, and impair our ability to generate revenue from product sales, regulatory and commercialization milestones and royalties. Moreover, 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.

Our failure to successfully complete clinical trials of our product candidates and to demonstrate the efficacy and safety necessary to obtain regulatory approval to market any of our product candidates would significantly harm our business.

***If we, or any collaborators, experience any of a number of possible unforeseen events in connection with clinical trials of our product candidates, potential clinical development, marketing approval or commercialization of our product candidates could be delayed or prevented.***

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, including testing in more subjects, 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;

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## [Table of Contents](#)

- 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 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.

Product development costs for us, or any collaborators, will increase if we, or they, experience delays in testing or pursuing marketing approvals and we, or they, may be required to obtain additional funds to complete clinical trials and prepare for possible commercialization of our product candidates. We do not know whether any preclinical tests or clinical trials will begin as planned, will need to be restructured, or will be completed on schedule or at all. Significant preclinical study or clinical trial delays also could shorten any periods during which we, or any future collaborators, may have the exclusive right to commercialize our product candidates or allow our competitors, or the competitors of any collaborators, to bring products to market before we, or any collaborators, do and impair our ability, or the ability of any collaborators, to successfully commercialize our product candidates and may harm our business and results of operations. In addition, many of the factors that lead to clinical trial delays may ultimately lead to the denial of marketing approval of any of our product candidates.

***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 or they 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.

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## [Table of Contents](#)

Utilizing our precision medicine approach, we focus our development activities on genetically or biomarker defined patients most likely to respond to our therapies. As a result, the potential patient populations for our clinical trials are narrowed, and we may experience difficulties in identifying and enrolling a sufficient number of patients in our clinical trials. In particular, the successful completion of our clinical development program for AG-348 for the treatment of PK deficiency is dependent upon our ability to enroll a sufficient number of patients with PK deficiency. PK deficiency is a rare disease with a small patient population. Further, there are only a limited number of specialist physicians that regularly treat patients with PK deficiency and major clinical centers that support PK deficiency are concentrated in a few geographic regions. The small population of patients, the nature of the disease and limited trial sites may make it difficult for us to enroll enough patients to complete our clinical trials for AG-348 for PK deficiency in a timely and cost-effective manner.

In addition, other companies are conducting clinical trials, or may in the future conduct clinical trials, which may have similar eligibility criteria as our current or future clinical trials. For example, Novartis International AG, or Novartis, is currently conducting a phase 1 clinical trial of its IDH1 mutant inhibitor, IDH305, in patients with advanced malignancies, and this trial and other trials may compete with our clinical trials of ivosidenib (AG-120) and/or AG-881 for eligible patients with hematological and/or other malignancies harboring an IDH1 mutation. Competition for these patients may make it particularly difficult for us to enroll enough patients to complete our clinical trials for ivosidenib (AG-120) or AG-881 in a timely and cost-effective manner.

Furthermore, we rely on contract research organizations, or 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 most advanced product candidates are still in 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. Adverse events or undesirable side effects caused by, or other unexpected properties of, our product candidates could cause us, any future collaborators, an institutional review board or regulatory authorities to interrupt, delay or halt clinical trials of one or more of our product candidates and could result in a more restrictive label, or the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities. If adverse effects were to arise in patients being treated with any of our product candidates, it could require us to halt, delay or interrupt clinical trials of such product candidate or adversely affect our ability to obtain requisite approvals to advance the development and commercialization of such product candidate. If any of our product candidates is associated with adverse events or undesirable side effects or has properties that are unexpected, we, or any future collaborators, may need to abandon development or limit development of that product candidate 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 earlier stage testing for treating cancer, RGDs or other diseases have later been found to cause side effects that prevented further development of the compound. For instance, in December 2016, we withdrew our investigational new drug application for AG-519, our second PKR activator, following verbal notification of a clinical hold from the FDA relating to a previously disclosed case of drug-induced cholestatic hepatitis which occurred in our phase 1 clinical trial of AG-519 in healthy volunteers. Although these decisions and this hepatic adverse event finding do not affect our ongoing global phase 2 clinical trial (DRIVE PK) for AG-348, our first PKR activator, we cannot provide any assurances that there will not be similar or other treatment-related severe adverse events in DRIVE PK or our other clinical trials, that our other trials will not be placed on clinical hold in the future, or that patient recruitment for DRIVE PK or our other trials will not be adversely impacted.

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[Table of Contents](#)

***Results of preclinical studies and early clinical trials may not be predictive of results of future clinical trials.***

The outcome of preclinical studies and early clinical trials may not be predictive of the success of later clinical trials, and interim results of clinical trials do not necessarily predict success in future clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in earlier development, and we could face similar setbacks. The design of a clinical trial can determine whether its results will support approval of a product and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. We have limited experience in designing clinical trials and may be unable to design and execute a clinical trial to support marketing approval. In addition, preclinical and clinical data are often susceptible to varying interpretations and analyses. Many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval for the product candidates. Even if we, or future collaborators, believe that the results of clinical trials for our product candidates warrant marketing approval, the FDA or comparable foreign regulatory authorities may disagree and may not grant marketing approval of our product candidates.

In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, changes in and adherence to the dosing regimen and other clinical trial protocols and the rate of dropout among clinical trial participants. If we fail to receive positive results in clinical trials of our product candidates, the development timeline and regulatory approval and commercialization prospects for our most advanced product candidates, and, correspondingly, our business and financial prospects would be negatively impacted.

***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.

***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 will 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 rely and expect to continue to rely in part or in whole on third parties for their design and manufacture. We also depend on Celgene for the development of companion diagnostics for

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## [Table of Contents](#)

some of our cancer therapeutic product candidates. If any parties, including without limitation Celgene or us, or any third parties engaged by Celgene or 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 of any of these events, our business would be harmed, possibly materially.

***We have never obtained marketing approval for a product candidate and we may be unable to obtain, or may be delayed in obtaining, marketing approval for any of our product candidates.***

We have never obtained marketing approval for a product candidate. Celgene submitted an NDA to the FDA for enasidenib in R/R AML in December 2016. We plan to explore a similar regulatory pathway for ivosidenib (AG-120), and we expect to submit a NDA ivosidenib (AG-120) in IDH1 mutant-positive R/R AML by the end of 2017. It is possible that the FDA may refuse to accept for substantive review any NDAs that we and/or Celgene submit for our product candidates, including the NDAs that Celgene submitted for enasidenib and that we plan to submit for ivosidenib (AG-120), or may conclude after review of our data that our application is insufficient to obtain marketing approval of our product candidates. If the FDA does not accept or approve our NDAs for any of our product candidates, it may require that we conduct additional clinical trials, preclinical studies or manufacturing validation studies and submit that data before it will reconsider our applications. Depending on the extent of these or any other FDA-required trials or studies, approval of any NDA or application that we submit may be delayed by several years, or may require us to expend more resources than we have available. It is also possible that additional trials or studies, if performed and completed, may not be considered sufficient by the FDA to approve our NDAs. Any delay in obtaining, or an inability to obtain, marketing approvals would prevent us from commercializing our product candidates, generating revenue and achieving and sustaining profitability. If any of these outcomes occur, we may be forced to abandon our development efforts for our product candidates, which could significantly harm our business.

***Even if any of our product candidates receives marketing approval, we or others may later discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, which could compromise our ability, or that of any future collaborators, to market the product.***

Clinical trials of our product candidates are conducted in carefully defined sets of patients who have agreed to enter into clinical trials. Consequently, it is possible that our clinical trials, or those of any future collaborator, may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any, or alternatively fail to identify undesirable side effects. If, following approval of a product candidate, we, or others, discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, any of the following adverse events could occur:

- regulatory authorities may withdraw their approval of the product or seize the product;
- we, or any future collaborators, may be required to recall the product, change the way the product is administered or conduct additional clinical trials;
- additional restrictions may be imposed on the marketing of, or the manufacturing processes for, the particular product;
- we may be subject to fines, injunctions or the imposition of civil or criminal penalties;

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## Table of Contents

- regulatory authorities may require the addition of labeling statements, such as a “black box” warning or a contraindication;
- we, or any future collaborators, may be required to create a Medication Guide outlining the risks of the previously unidentified side effects for distribution to patients;
- we, or any future collaborators, could be sued and held liable for harm caused to patients;
- the product may become less competitive; and
- our reputation may suffer.

***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 revenue 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;
- ensuring uninterrupted product supply;
- the strength of marketing and distribution support;
- sufficient third-party coverage or reimbursement; and
- the prevalence and severity of any side effects.

***If 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 have little 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. We are in the early stages of building a 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.

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## [Table of Contents](#)

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 revenue or the profitability of product revenue 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 AML and high risk myelodysplasia. For example, Jazz Pharmaceuticals plc, Novartis, Seattle Genetics, Inc. and Abbvie Inc. (in collaboration with Roche Holdings Inc., or Roche) are each developing therapies to treat AML. Some 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 most of 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

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## [Table of Contents](#)

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 marketing approval.

There are also a number of product candidates in preclinical or clinical 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 and its subsidiary Genentech, Inc., GlaxoSmithKline plc, Merck & Co., Novartis with its IDH1 mutant inhibitor IDH305, Pfizer, Inc., and Genzyme, a Sanofi company. There are also biotechnology companies of various sizes 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 with its IDH1 mutant inhibitor FT-2102, Shire Biochem Inc., Raze Therapeutics, Inc. and Selvita S.A. In addition, there are several companies developing immunotherapies, including metabolic immunotherapies, targeting cancer, including AstraZeneca PLC, Merck, Bristol-Myers Squibb Company and Novartis. 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 clinical 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 commercial success of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by third-party payors, including government health administration authorities and private health coverage insurers. If coverage and reimbursement is not available, or reimbursement is available only to limited levels, we, or any future collaborators, may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us, or any future collaborators, to establish or maintain pricing sufficient to realize a sufficient return on our or their investments. In the United States, no uniform policy of coverage and reimbursement for products exists among third-party payors and coverage and reimbursement for products can differ significantly from payor to payor. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

There is significant uncertainty related to third-party payor coverage and reimbursement of newly approved drugs. Marketing approvals, pricing and reimbursement for new drug products vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign

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## [Table of Contents](#)

markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we, or any future collaborators, might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay commercial launch of the product, possibly for lengthy time periods, which may negatively impact the revenue we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability or the ability of any future collaborators to recoup our or their investment in one or more product candidates, even if our product candidates obtain marketing approval.

Patients who are provided medical treatment for their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Therefore, our ability, and the ability of any future collaborators, to commercialize any of our product candidates will depend in part on the extent to which coverage and reimbursement for these products and related treatments will be available from third-party payors. Third-party payors decide which medications they will cover and establish reimbursement levels. The healthcare industry is acutely focused on cost containment, both in the United States and elsewhere. Government authorities and other third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications, which could affect our ability or that of any future collaborators to sell our product candidates profitably. These payors may not view our products, if any, as cost-effective, and coverage and reimbursement may not be available to our customers, or those of any future collaborators, or may not be sufficient to allow our products, if any, to be marketed on a competitive basis. Cost-control initiatives could cause us, or any future collaborators, to decrease the price we, or they, might establish for products, which could result in lower than anticipated product revenue. If the prices for our products, if any, decrease or if governmental and other third-party payors do not provide coverage or adequate reimbursement, our prospects for revenue and profitability will suffer.

There may also be delays in obtaining coverage and reimbursement for newly approved drugs, and coverage may be more limited than the indications for which the drug is approved by the FDA or comparable foreign regulatory authorities. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale and distribution. Reimbursement rates may vary, by way of example, according to the use of the product and the clinical setting in which it is used. Reimbursement rates may also be based on reimbursement levels already set for lower cost drugs or may be incorporated into existing payments for other services.

In addition, increasingly, third-party payors are requiring higher levels of evidence of the benefits and clinical outcomes of new technologies and are challenging the prices charged. We cannot be sure that coverage will be available for any product candidate that we, or any future collaborator, commercialize and, if available, that the reimbursement rates will be adequate. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. An inability to promptly obtain coverage and adequate payment rates from both government-funded and private payors for any of our product candidates for which we, or any future collaborator, obtain marketing approval could significantly harm our operating results, our ability to raise capital needed to commercialize products 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;

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## [Table of Contents](#)

- 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;
- reduced resources of our management to pursue our business strategy; 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 as we advance or expand our 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

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## [Table of Contents](#)

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 collaborations 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.*

We are party to several collaboration agreements. These collaborations involve complex allocations of rights, provide for milestone payments to us based on the achievement of specified clinical development, regulatory and commercial milestones, provide us with royalty-based revenue if certain product candidates are successfully commercialized and provide for cost reimbursements of certain development activities. We cannot predict the success of these collaborations.

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 revenue 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 collaborations, 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 the 2010 Agreement, the AG-881 Agreements and programs under a co-development and co-commercialization agreement pursuant to the 2016 Agreement, development and commercialization plans and strategies for licensed programs, such as enasidenib, 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, as to which Celgene may have 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, under the 2016 Agreement, 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 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, which may result in a need for additional capital to pursue further development or commercialization of the applicable product candidate. For example, under the 2010 Agreement and the 2016 Agreement, 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.

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## Table of Contents

- Collaborators 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, under specified circumstances Celgene has the first right to maintain or defend our intellectual property rights with respect to enasidenib under the 2010 Agreement 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 agreements 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 agreements with us, in their entirety or with respect to enasidenib under the 2010 Agreement or any program under the 2016 Agreement, upon 90 days' notice and can terminate each entire agreement with us in connection with a material breach of the agreement by us that remains uncured for a period ranging from 60 to 90 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 collaborators 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 the 2016 Agreement, we may not directly or indirectly develop, manufacture or commercialize, except pursuant to the agreement, any

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## [Table of Contents](#)

medicine or product candidate with specified activity against certain metabolic targets except in connection with certain third-party collaborations or with respect to certain targets the rights to which have reverted back to us pursuant to the terms of the 2016 Agreement. Following the discovery phase until termination or expiration of the 2010 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. Following the discovery phase of the 2016 Agreement until termination or expiration of the applicable co-development and co-commercialization agreement or license agreement under the 2016 Agreement, we may not directly or indirectly develop, manufacture or commercialize, outside of the collaboration, any medicine or product candidate with specified activity against the collaboration target that is the subject of such co-development and co-commercialization agreement or license agreement, except in connection with certain third-party collaborations or with respect to certain targets the rights to which have reverted back to us pursuant to the terms of the 2016 Agreement.

Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of 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 do not independently conduct clinical trials of any of our product candidates. We rely and expect to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials. In addition 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 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 responsibility to comply with any such standards. 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

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## [Table of Contents](#)

Area 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 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 U.S. government-sponsored database, [clinicaltrials.gov](http://clinicaltrials.gov), within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Furthermore, third parties on whom we rely 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 revenue could be delayed.

We also rely and expect to continue 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 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 our product candidates for our ongoing preclinical and clinical 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 long-term supply 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

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## [Table of Contents](#)

- reliance on the third party for regulatory compliance, quality assurance, environmental and safety and pharmacovigilance reporting.

Third-party manufacturers may not be able to comply with cGMP regulations or similar regulatory requirements on a global basis. 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 manufacturers 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 do not yet have issued patents for all our most advanced product candidates in all markets we intend to commercialize.

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

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## [Table of Contents](#)

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 that protect our technology or medicines or that 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 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.

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## [Table of Contents](#)

***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. We are not aware of any other legal proceedings having 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 collaborators may not be able to obtain any required license on commercially reasonable terms or at all. Even if we or our collaborators 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.

***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

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## [Table of Contents](#)

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**

***Even if we complete the necessary preclinical studies and clinical trials, the marketing approval process is expensive, time-consuming and uncertain and may prevent us from obtaining approvals for the commercialization of some or all of our product candidates. 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, export and import, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the EMA and comparable regulatory 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 marketing 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.

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## [Table of Contents](#)

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.

Accordingly, 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 revenue 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, enasidenib and ivosidenib (AG-120) received fast track designation for treatment of patients with acute myelogenous leukemia, or AML, that harbor an IDH2 and IDH1 mutation, respectively. 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 may decide not to grant it. Even though enasidenib and ivosidenib (AG-120) have received fast track designation for treatment of patients with AML that harbor an IDH2 and IDH1 mutation, respectively, we may not experience a faster development process, review or approval, if at all, 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 foreign jurisdictions would prevent our medicines from being marketed in such jurisdictions.***

In order to market and sell our medicines in the European Union, or EU, 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, a product must 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.

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## [Table of Contents](#)

***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 substantial 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 and manufacturing, 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, including the requirement to implement a risk evaluation and mitigation strategy.

The FDA and other agencies, including the Department of Justice, or the DOJ, closely regulate and monitor the post-approval marketing and promotion of products to ensure that they are marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA and DOJ impose 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. Violations of the Federal Food, Drug, and Cosmetic Act and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription drugs may lead to investigations and enforcement actions alleging violations of federal and state health care fraud and abuse laws, as well as state consumer protection laws.

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

- restrictions on such medicine, 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 studies or clinical trials;
- warning letters or untitled letters;
- withdrawal of the medicine from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of medicines;
- damage to relationships with any potential collaborators;
- unfavorable press coverage and damage to our reputation;
- 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;
- injunctions or the imposition of civil or criminal penalties; and
- litigation involving patients using our medicines.

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## [Table of Contents](#)

Non-compliance with EU requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with the EU requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

***Our relationships with healthcare providers, physicians and third-party payors will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which, in the event of a violation, 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 will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our future arrangements with healthcare providers, physicians and third-party payors 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 any medicines for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal 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, or in return for, either the referral of an individual for, or the purchase, order or recommendation or arranging of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;
- the federal False Claims Act imposes criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties, currently set at \$10,781.40 to \$21,562.80 per false claim;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal Physician Payments Sunshine Act requires applicable manufacturers of covered drugs to report payments and other transfers of value to physicians and teaching hospitals, with data collection beginning in August 2013; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws and transparency statutes, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers.

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 and may require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

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## [Table of Contents](#)

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, imprisonment, exclusion of products 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 healthcare 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.

***Current and future legislation may increase the difficulty and cost for us and any future collaborators to obtain marketing approval of our other 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, among other things, prevent or delay marketing approval of our other product candidates, restrict or regulate post-approval activities and affect our ability, or the ability of any future collaborators, to profitably sell any products for which we, or they, obtain marketing approval. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and additional downward pressure on the price that we, or any future collaborators, may receive for any approved products.

For example, in March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the PPACA. Among the provisions of the PPACA of potential importance to our business and our product candidates are the following:

- an annual, non-deductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program;
- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;
- expansion of healthcare fraud and abuse laws, including the civil False Claims Act and the federal Anti-Kickback Statute, new government investigative powers and enhanced penalties for noncompliance;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability to individuals enrolled in Medicaid managed care organizations;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- new requirements to report certain financial arrangements with physicians and teaching hospitals;
- a new requirement to annually report drug samples that manufacturers and distributors provide to physicians;

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## [Table of Contents](#)

- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- a new Independent Payment Advisory Board, or IPAB, which has authority to recommend certain changes to the Medicare program to reduce expenditures by the program that could result in reduced payments for prescription drugs; and
- a Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models.

Other legislative changes have been proposed and adopted since the PPACA was enacted. These changes include the Budget Control Act of 2011, which, among other things, led to aggregate reductions to Medicare payments to providers of up to 2% per fiscal year that started in 2013 and, due to subsequent legislation, will continue until 2025. In addition, the American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and may otherwise affect the prices we may obtain for any of our product candidates for which regulatory approval is obtained.

We expect that the PPACA, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and additional downward pressure on the price that we receive for any approved product. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our medicines.

In addition, with the new Administration and Congress, there will likely be additional legislative changes, including repeal and replacement of certain provisions of the PPACA. It remains to be seen, however, precisely what the new legislation will provide, when it will be enacted and what impact it will have on the availability of healthcare and containing or lowering the cost of healthcare. Such reforms could have an adverse effect on anticipated revenue from product candidates that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop product candidates.

Moreover, 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 and any future collaborators 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 key executives and scientific leadership and to attract, retain and motivate qualified personnel.*

We are highly dependent on the principal members of our management and scientific teams, each of whom is 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

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## [Table of Contents](#)

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 healthcare 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 Conduct and 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.

***We may engage in acquisitions that could disrupt our business, cause dilution to our stockholders or reduce our financial resources.***

In the future, we may enter into transactions to acquire other businesses, products or technologies. Because we have not made any acquisitions to date, our ability to do so successfully is unproven. If we do identify suitable candidates, we may not be able to make such acquisitions on favorable terms, or at all. Any acquisitions we make may not strengthen our competitive position, and these transactions may be viewed negatively by customers or investors. We may decide to incur debt in connection with an acquisition or issue our common stock or other equity securities to the stockholders of the acquired company, which would reduce the percentage ownership of our existing stockholders. We could incur losses resulting from undiscovered liabilities of the acquired business that are not covered by the indemnification we may obtain from the seller. In addition, we may not be able to successfully integrate the acquired personnel, technologies and operations into our existing business in an effective, timely and non-disruptive manner. Acquisitions may also divert management attention from day-to-day responsibilities, increase our expenses and reduce our cash available for operations and other uses. We cannot predict the number, timing or size of future acquisitions or the effect that any such transactions might have on our operating results.

## **Risks Related to Our Common Stock**

***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 to sell their shares at all.

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## [Table of Contents](#)

An 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 is likely to be volatile, 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. For example, since January 1, 2014 the price of our common stock on the NASDAQ Global Select Market has ranged from \$21.70 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:

- regulatory actions with respect to our product candidates or our competitors' products and product candidates;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures, collaborations or capital commitments;
- the timing and results of clinical trials of product candidates;
- commencement or termination of collaborations for our development programs;
- failure or discontinuation of any of our development programs;
- results of clinical trials of product candidates 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 develop additional product candidates or products;
- actual or anticipated changes in estimates as to financial results or development timelines;
- announcement or expectation of additional financing efforts;
- sales of our common stock by us, our insiders or other stockholders;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in estimates or recommendations by securities analysts, if any, that cover our stock;
- 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.***

Certain stockholders hold a substantial number of shares of our common stock. If such stockholders 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.

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## [Table of Contents](#)

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 who have exercised registration rights could have a material adverse effect on the trading price of our common stock.

***Our executive officers, directors and principal stockholders maintain the ability to significantly influence all matters submitted to stockholders for approval.***

As of December 31, 2016, our executive officers, directors and a small group of stockholders, in the aggregate, beneficially owned shares representing a significant percentage of our capital stock. As a result, if these stockholders were to choose to act together, they would be able to significantly influence 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, could significantly influence 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.

***Future sales and issuances of our common stock or rights to purchase common stock 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.

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

We have incurred and will continue to incur significant legal, accounting and other expenses as a public 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

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## [Table of Contents](#)

regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations increase our legal and financial compliance costs and make some activities more time-consuming and costly.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, we are required to furnish with our periodic Exchange Act reports a report by our management on our internal control over financial reporting and 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 maintain compliance with Section 404, we 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 a preexisting lease under which we leased 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 First Amendment, to expand the rentable square footage of the leased space at 88 Sidney Street to approximately 113,200 square feet. Our lease at 38 Sidney Street terminated on June 15, 2015. On July 20, 2015, we entered into a second amendment to the Lease, or the Second Amendment, to expand the rentable square footage at 88 Sidney Street to approximately 146,030 square feet. The initial term of the Lease, including First Amendment and Second Amendment, will terminate on May 15, 2022. At the end of the initial 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**

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

### **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 years ended December 31, 2016 and 2015.

<b>2016</b>	<b>High</b>	<b>Low</b>
First Quarter	\$ 66.87	\$ 33.50
Second Quarter	\$ 66.74	\$ 39.36
Third Quarter	\$ 54.99	\$ 35.84
Fourth Quarter	\$ 67.74	\$ 40.59

<b>2015</b>	<b>High</b>	<b>Low</b>
First Quarter	\$ 138.85	\$ 88.03
Second Quarter	\$ 126.35	\$ 90.58
Third Quarter	\$ 120.96	\$ 67.52
Fourth Quarter	\$ 81.77	\$ 48.00

**Holders**

As of February 14, 2017, there were approximately 16 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.

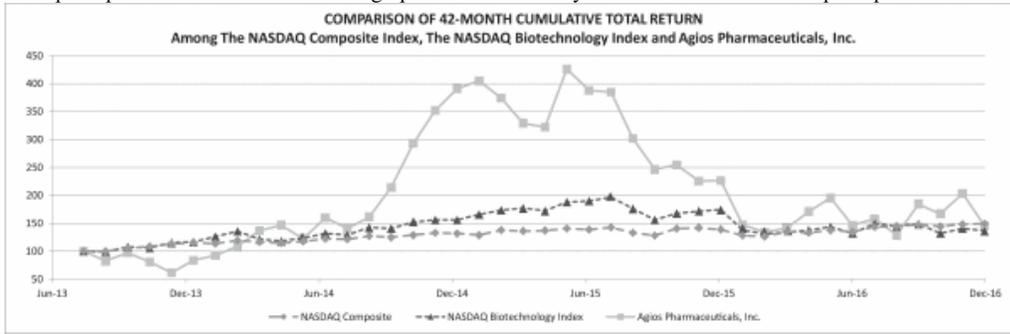
**Performance Graph**

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, 2016. 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

[Table of Contents](#)

dividends, if any. The stock price performance included in this graph is not necessarily indicative of future stock price performance.



**Recent Sales of Unregistered Securities**

None.

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

Neither we nor any affiliated purchaser or anyone acting on behalf of us or an affiliated purchaser made any purchases of shares of our common stock during the fourth quarter of 2016.

[Table of Contents](#)

**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, 2016, 2015 and 2014 and the consolidated balance sheet data as of December 31, 2016 and 2015 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 years ended December 31, 2013 and 2012 and the consolidated balance sheet data as of December 31, 2014, 2013 and 2012 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.

(in thousands, except share and per share amounts)	Year Ended December 31,				
	2016	2015	2014	2013	2012
<b>Consolidated statements of operations:</b>					
Collaboration revenue – related party(1)	\$ 69,892	\$ 59,119	\$ 65,358	\$ 25,548	\$ 25,106
Operating expenses:					
Research and development (net of \$19,714 and \$25,173 of cost reimbursement from related party for the years ended December 31, 2016 and 2015, respectively)	220,163	141,827	100,371	54,502	41,037
General and administrative	50,714	35,992	19,120	9,929	7,064
Total operating expenses	<u>270,877</u>	<u>177,819</u>	<u>119,491</u>	<u>64,431</u>	<u>48,101</u>
Loss from operations	(200,985)	(118,700)	(54,133)	(38,883)	(22,995)
Interest income	2,514	968	203	55	69
Loss before (benefit) provision for income taxes	(198,471)	(117,732)	(53,930)	(38,828)	(22,926)
(Benefit) provision for income taxes	—	—	(426)	579	(2,824)
Net loss	(198,471)	(117,732)	(53,504)	(39,407)	(20,102)
Cumulative preferred stock dividends	—	—	—	(4,162)	(7,190)
Net loss applicable to common stockholders	<u>\$ (198,471)</u>	<u>\$ (117,732)</u>	<u>\$ (53,504)</u>	<u>\$ (43,569)</u>	<u>\$ (27,292)</u>
Net loss per share applicable to common stockholders – basic and diluted	<u>\$ (5.07)</u>	<u>\$ (3.15)</u>	<u>\$ (1.59)</u>	<u>\$ (2.83)</u>	<u>\$ (8.02)</u>
Weighted-average number of common shares used in net loss per share applicable to common stockholders – basic and diluted	<u>39,126,400</u>	<u>37,429,262</u>	<u>33,667,024</u>	<u>15,415,373</u>	<u>3,401,719</u>

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[Table of Contents](#)

- (1) In July 2014, April 2015 and May 2016 we amended our collaboration agreements. Refer to the discussion in Note 3 to the consolidated financial statements appearing elsewhere in this Annual Report for further explanation of the amendments' impact on collaboration revenue.

(in thousands)	December 31,				
	2016	2015	2014	2013(1)	2012
<b>Consolidated Balance Sheet Data:</b>					
Cash, cash equivalents and marketable securities	\$ 573,564	\$ 375,907	\$ 467,447	\$ 193,894	\$ 127,976
Total assets	619,094	420,065	491,904	201,205	137,008
Total liabilities	260,503	74,947	67,538	69,723	93,110
Convertible preferred stock	—	—	—	—	115,922
Common stock	42	38	37	31	3
Additional paid-in capital	842,013	630,078	591,334	244,881	2,012
Accumulated deficit	(483,151)	(284,680)	(166,948)	(113,444)	(74,037)
Total stockholders' equity (deficit)	358,591	345,118	424,366	131,482	(72,024)

- (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 the fundamental transformation of patients’ lives through scientific leadership in the fields of cancer and rare genetic metabolic disorders. 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. Our therapeutic areas of focus are cancer and rare genetic metabolic disorders, 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 as a platform to create transformative therapies. Our most advanced cancer product candidates are enasidenib and ivosidenib (AG-120), which target mutated isocitrate dehydrogenase 2 and 1, or IDH2 and IDH1, respectively, and AG-881, which targets both mutated IDH1 and mutated IDH2. These mutations are found in a wide range of hematological malignancies and solid tumors. The lead product candidate in our rare genetic metabolic disorder, or RGD, programs, 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.

### **2016 Agreement**

In May 2016, we entered into a master research and collaboration agreement, or the 2016 Agreement, with Celgene and Celgene RIVOT Ltd., a wholly owned subsidiary of Celgene. The 2016 Agreement establishes a new global collaboration focused on the research and development of immunotherapies against certain metabolic targets that exert their antitumor efficacy primarily via the immune system. In addition to new programs identified under the 2016 Agreement, Celgene and we have also agreed that all future development and commercialization of two remaining cancer metabolism programs discovered under the 2010 discovery and development collaboration and license agreement with Celgene, or the 2010 Agreement, including a program focused on methylthioadenosine phosphorylase, or MTAP, deleted cancers, will now be governed by the 2016 Agreement.

During the research term of the 2016 Agreement, we plan to conduct research programs focused on discovering compounds that are active against metabolic targets in the immuno-oncology, or IO, field. The initial four-year research term will expire on May 17, 2020. The research term may be extended for up to two or, in specified cases, up to four additional one-year terms by paying us a \$40.0 million per year extension fee.

For each program under the 2016 Agreement, we may nominate compounds that meet specified criteria as development candidates, and, in limited circumstances, Celgene may also nominate compounds as development candidates for each such program. Celgene may designate the applicable program for further development following any such nomination, after which we may conduct, at our expense, additional pre-clinical and clinical development for such program through completion of an initial phase 1 dose escalation study.

At the end of the research term, Celgene may designate for continued development up to three research programs for which development candidates have yet to be nominated, which we refer to as continuation programs. We may conduct further research and pre-clinical and clinical development activities on any continuation program, at our expense, through completion of an initial phase 1 dose escalation study.

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## [Table of Contents](#)

We have granted Celgene the right to obtain exclusive options to development and commercialization rights for each program that Celgene has designated for further development, and for each continuation program. Celgene may exercise each such option beginning upon the designation of a development candidate for such program (or upon the designation of such program as a continuation program) and ending on the earlier of (i) the end of a specified period after we have furnished Celgene with specified information about the initial phase 1 dose escalation study for such program, or (ii) January 1, 2030. Research programs that have applications in the inflammation or autoimmune, or I&I, field that may result from the 2016 Agreement will also be subject to the exclusive options described above.

We will retain rights to any program that Celgene does not designate for further development or as to which it does not exercise its option.

Under the terms of the 2016 Agreement, following Celgene's exercise of its option with respect to a program, the parties will enter into either a co-development and co-commercialization agreement if such program is in the IO field, or a license agreement if such program is in the I&I field. Under each co-development and co-commercialization agreement, the parties will co-develop and co-commercialize licensed products worldwide. Either we or Celgene will lead development and commercialization of licensed products for the United States and Celgene will lead development and commercialization of licensed products outside of the United States. Depending on the country, the parties will each have the right to provide a portion of field-based marketing activities. Under each license agreement, Celgene will have the sole right to develop and commercialize licensed products worldwide.

### ***AG-120 Letter Agreement***

Also in May 2016, the parties agreed to terminate the 2010 Agreement, effective as of August 15, 2016, as to the program directed to the IDH1 target, for which ivosidenib (AG-120) is the lead development candidate. Under the 2010 Agreement, Celgene had held development and commercialization rights to the IDH1 program outside of the United States, and we held such rights inside the United States. As a result of the termination, we obtained global rights to ivosidenib (AG-120) and the IDH1 program. Neither party will have any further financial obligation, including royalties or milestone payments, to the other concerning ivosidenib (AG-120) or the IDH1 program. Under the terms of the termination, the parties are released from their exclusivity obligations under the 2010 Agreement with respect to the IDH1 program. The ivosidenib (AG-120) termination does not affect the AG-881 Agreements, which are directed at both the IDH1 target and the IDH2 target.

### ***AG-881 Agreements***

During April 2015, we selected a third novel IDH mutant inhibitor, AG-881, for clinical development. On April 27, 2015, we entered into a joint worldwide development and profit share collaboration and license agreement with Celgene; our wholly owned subsidiary, Agios International Sarl, which was organized in Switzerland in April 2015, entered into a collaboration and license agreement with Celgene International II Sarl. Both of these agreements are collectively referred to as the AG-881 Agreements. The AG-881 Agreements establish a worldwide collaboration focused on the development and commercialization of AG-881 products. Under the terms of the AG-881 Agreements, we received initial upfront payments totaling \$10.0 million in May 2015 and are eligible to receive up to \$70.0 million in milestone-based payments. The parties will equally split all worldwide development costs, subject to specified exceptions, as well as any profits from any net sales of, or commercialization losses related to, licensed AG-881 products.

### ***2010 Agreement***

In April 2010, we entered into the 2010 Agreement, with a focus on targeting cancer metabolism. The goal of the collaboration under the 2010 Agreement was to discover, develop and commercialize disease-altering therapies in oncology based on our cancer metabolism research platform that have achieved development candidate

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## [Table of Contents](#)

status. We initially led research, preclinical and early clinical development for all cancer metabolism programs under the collaboration. The discovery phase of the collaboration under the 2010 Agreement expired in April 2016.

Under the terms of the 2010 Agreement, Celgene leads and funds global development and commercialization of enasidenib, the sole remaining program under the 2010 Agreement, for which it exercised its option to obtain a co-commercialization license. We are eligible to receive up to \$120.0 million in milestone-based payments as well as royalties on any sales on enasidenib; in January 2016, we earned a \$25.0 million milestone upon the achievement of a specified clinical development event.

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 the 2010 Agreement, the AG-881 Agreements, the 2016 Agreement, private placements of our preferred stock, our initial public offering 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 received from Celgene.

Since inception, we have incurred significant operating losses. Our net losses were \$198.5 million, \$117.7 million and \$53.5 million for the years ended December 31, 2016, 2015 and 2014, respectively. As of December 31, 2016, we had an accumulated deficit of \$483.2 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, enasidenib, ivosidenib (AG-120), AG-881 and AG-348; continue to discover and validate novel targets and drug product candidates; expand and protect our intellectual property portfolio; and hire additional commercial, development and scientific personnel.

### **Financial Operations Overview**

#### ***Revenue***

Through December 31, 2016, we have not generated any revenue from product sales. Substantially all of our revenue to date has been derived from our collaborations. In the future, we will seek to generate revenue from a combination of product sales, upfront payments, cost reimbursements, milestone payments, and royalties on future product sales.

#### *Collaboration and license revenue*

Arrangement consideration is 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 the Financial Accounting Standards Board's (FASB) Accounting Standards Codification (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.

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 our 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 trial approvals and the estimated patient populations.

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## [Table of Contents](#)

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

### *Milestone revenue*

We 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. At the inception of each arrangement that includes milestone payments, we evaluate each contingent payment on an individual basis to determine whether it is considered a substantive milestone, 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.

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

### *Research and development expenses*

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, 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 and commercialize these product candidates. We are also unable to predict when, if ever, material net cash inflows will commence from enasidenib, ivosidenib (AG-120), AG-881, 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 and/or new drug application, or NDA, enabling toxicology studies;
- the successful enrollment in, and completion of, clinical trials;
- the receipt of marketing approvals from applicable regulatory authorities;
- establishing compliant 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.

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## [Table of Contents](#)

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. Reimbursements received under our collaboration agreements for certain costs for which we are not the principal in the transaction according to the provisions of ASC 605-45 are recorded as a reduction to research and development expense.

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

### ***Enasidenib***

Enasidenib 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. In December 2016, our partner Celgene submitted a NDA, to the U.S. Food and Drug Administration, or FDA, for enasidenib in relapsed and/or refractory AML, or R/R AML. The NDA is based on data from the ongoing phase 1/2 study of enasidenib in patients with advanced hematologic malignancies with an IDH2 mutation. In June 2014, the FDA granted us orphan drug designation for enasidenib for treatment of patients with AML and in August 2014, we announced that the FDA granted fast track designation to enasidenib for treatment of patients with AML that harbor an IDH2 mutation. In April 2016, we and Celgene received European Medicines Agency, or EMA, orphan drug designation for enasidenib for the treatment of AML. We continue to evaluate enasidenib in clinical trials evaluating hematological cancers with IDH2 mutations. To date, all clinical data reported by us and our collaborators in hematological cancers highlights that the mechanism of response is consistent with preclinical studies, including substantial reduction of plasma 2-hydroxygluturate, or 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.

Celgene maintains worldwide development and commercial rights to enasidenib and Celgene will fund the future development and commercialization costs related to this program. Under the 2010 Agreement, Celgene is responsible for all development costs for enasidenib, and we are eligible to receive up to \$120.0 million in milestone payments and a tiered royalty on any net sales of products containing enasidenib. In January 2016, we earned a \$25.0 million milestone payment upon initiation of the IDHENTIFY clinical trial, as described below. In addition to contributing our scientific and translational expertise, we will continue to conduct some clinical development and regulatory activities within the enasidenib development program under the 2010 Agreement. We also have co-commercialization rights to provide up to one-third of the commercialization efforts and will be reimbursed for those efforts.

We and Celgene are evaluating enasidenib in the following clinical trials:

- A phase 1/2 multicenter, open-label, clinical trial to assess the safety, clinical activity, and tolerability of enasidenib in patients with advanced hematologic malignancies with an IDH2 mutation. The trial

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## [Table of Contents](#)

includes a dose-escalation phase and the following five expansion cohorts, all of which have completed accrual: (i) a cohort of 25 patients aged 60 years or older with IDH2 mutant-positive R/R AML, or any IDH2-mutant positive AML patient, regardless of age, who has relapsed following a bone marrow transplant, or BMT; (ii) a cohort of 25 patients aged less than 60 years with IDH2 mutant-positive R/R AML, not including patients with AML who have relapsed following a BMT; (iii) a cohort of 25 patients aged 60 years or older with untreated IDH2 mutant-positive AML who decline standard of care chemotherapy; (iv) a cohort of 25 patients with IDH2 mutant-positive advanced hematologic malignancies not eligible for cohorts for the previous three cohorts; and (v) a cohort of approximately 125 patients with IDH2 mutant-positive AML who are in second or later relapse, refractory to second-line induction or reinduction treatment, or have relapsed after allogeneic transplantation.

- IDHENTIFY, an international phase 3, multi-center, open-label, randomized clinical trial designed to compare the efficacy and safety of enasidenib versus conventional care regimens in patients 60 years or older with IDH2 mutant-positive AML that is refractory to or relapsed after second- or third-line therapy. In January 2016, in conjunction with the initiation of the IDHENTIFY clinical trial, we received a milestone payment of \$25.0 million from Celgene pursuant to the 2010 Agreement.
- A phase 1b, multicenter, international, open-label clinical trial to evaluate the safety and clinical activity of enasidenib or ivosidenib (AG-120) in combination with induction and consolidation therapy in patients with newly diagnosed AML with an IDH2 or IDH1 mutation who are eligible for intensive chemotherapy. The trial will evaluate continuous dosing for up to one year with enasidenib administered at an initial oral dose of 100 mg once daily in patients with an IDH2 mutation or ivosidenib (AG-120) administered at an initial oral dose of 500 mg once daily in patients with an IDH1 mutation. Enasidenib or ivosidenib (AG-120) will be administered with two types of AML induction therapies (cytarabine with either daunorubicin or idarubicin) and two types of AML consolidation therapies (mitoxantrone with etoposide [ME] or cytarabine).
- A phase 1/2 frontline combination clinical trial, conducted by Celgene, of either enasidenib or ivosidenib (AG-120) in combination with VIDAZA® (azacitidine) in newly diagnosed AML patients not eligible for intensive chemotherapy, with a phase 1 component to determine the safety of the combinations, followed by a phase 2 randomized component evaluating the safety and clinical activity of each investigational combination versus single-agent VIDAZA® using a primary endpoint of overall response rate.

Celgene maintains worldwide development and commercial rights to enasidenib and it will fund the future development and commercialization costs related to this program.

### ***Ivosidenib (AG-120)***

Ivosidenib (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, cholangiocarcinoma, and glioma where both the treatment options and prognosis for patients are poor. On May 18, 2015, we announced that the FDA granted fast track designation to ivosidenib (AG-120) for treatment of patients with AML that harbor an IDH1 mutation. On June 10, 2015, the FDA granted us orphan drug designation for ivosidenib (AG-120) for treatment of patients with AML. In November 2016, the FDA granted fast-track designation to ivosidenib (AG-120) for treatment of patients with previously treated, unresectable or metastatic cholangiocarcinoma with and IDH1 mutation. In January 2017, we announced that we intend to submit an NDA to the FDA for ivosidenib (AG-120) in R/R AML by the end of 2017.

We are evaluating ivosidenib (AG-120) in the following clinical trials:

- A phase I multicenter, open-label, dose-escalation and expansion clinical trial for ivosidenib (AG-120), designed to assess its safety, clinical activity and tolerability as a single agent in patients with advanced

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## [Table of Contents](#)

hematologic malignancies with an IDH1 mutation. Four expansion cohorts have been added to the trial. The first cohort will evaluate 125 AML patients who are in second or later relapse, are refractory to second-line induction or reinduction treatment, or have relapsed after allogeneic transplantation. The second cohort will evaluate 25 untreated AML patients. The third cohort will evaluate 25 patients with other non-AML IDH1 mutant-positive relapsed or refractory advanced hematologic malignancies. The fourth cohort will evaluate patients with relapsed IDH1 mutant-positive AML not eligible for the first arm or standard of care chemotherapy. Ivosidenib (AG-120) is administered at a 500 mg once daily oral dose, in 28-day cycles.

- A phase 1 multicenter, open-label, dose-escalation and expansion clinical trial for ivosidenib (AG-120), designed to assess its safety, clinical activity and tolerability as a single agent in patients with advanced solid tumors with an IDH1 mutation, including glioma, intrahepatic cholangiocarcinoma, or IHCC, and chondrosarcomas. Enrollment is now complete for four expansion cohorts of 25 patients each in (i) low grade glioma with at least six months of prior scans to assess volumetric changes, (ii) second-line cholangiocarcinoma, (iii) high grade, or metastatic, chondrosarcoma, and (iv) other solid tumors with an IDH1 mutation, who will receive the recommended dose of 500 mg of ivosidenib (AG-120) once daily.
- ClarIDHy, a registration-enabling phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial of ivosidenib (AG-120) in previously-treated patients with nonresectable or metastatic cholangiocarcinoma with an IDH1 mutation. The trial was initiated in December of 2016.
- A phase 1b, multicenter, international, open-label clinical trial to evaluate the safety and clinical activity of enasidenib or ivosidenib (AG-120) in combination with induction and consolidation therapy in patients with newly diagnosed AML with an IDH2 or IDH1 mutation who are eligible for intensive chemotherapy. The trial is evaluating continuous dosing for up to one year with enasidenib administered at an initial oral dose of 100 mg once daily in patients with an IDH2 mutation or ivosidenib (AG-120) administered at an initial oral dose of 500 mg once daily in patients with an IDH1 mutation. Enasidenib or ivosidenib (AG-120) will be administered with two types of AML induction therapies (cytarabine with either daunorubicin or idarubicin) and two types of AML consolidation therapies (mitoxantrone with etoposide [ME] or cytarabine).
- A phase 1/2 frontline combination clinical trial, conducted by Celgene, of either enasidenib or ivosidenib (AG-120) in combination with VIDAZA® (azacitidine) in newly diagnosed AML patients not eligible for intensive chemotherapy. The phase 1 component will determine the safety of the combinations, followed by a phase 2 randomized component evaluating the safety and clinical activity of each investigational combination versus single-agent VIDAZA® using a primary endpoint of overall response rate.

In the first half of 2017, we intend to initiate AGILE, a global, registration-enabling phase 3 clinical trial combining ivosidenib (AG-120) and VIDAZA® in newly diagnosed AML patients with an IDH1 mutation ineligible for intensive chemotherapy.

Upon termination of the 2010 Agreement, effective as of August 15, 2016, as to the program directed to the IDH1 target, for which ivosidenib (AG-120) is the lead development candidate, we obtained global development and commercial rights to ivosidenib (AG-120) and the IDH1 program and expect to fund the future development and commercialization costs related to the program. Neither party has any further financial obligation, including royalties or milestone payments, to the other concerning ivosidenib (AG-120) or the IDH1 program.

### ***AG-881: brain penetrant pan-IDH program***

AG-881 is an orally available, selective, brain-penetrant, pan-IDH mutant inhibitor, which provides added flexibility to our current portfolio of IDH mutant inhibitors. We and Celgene are jointly collaborating on a worldwide development program, wherein we share worldwide development costs and profits and Celgene would book any worldwide commercial sales. We will lead commercialization in the United States with both

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## [Table of Contents](#)

companies sharing equally in field-based commercial activities, and Celgene will lead commercialization outside of the United States with us providing one third of field-based commercial activities in the major EU markets. Under the AG-881 Agreements, we are eligible to receive up to \$70.0 million in potential milestone payments related to AG-881. We may also receive royalties at tiered, low- to mid-teen percentage rates on net sales if Celgene elects to not participate in the development and commercialization of AG-881.

We are conducting two phase 1 multi-center, open-label clinical trials of AG-881, one in patients with advanced IDH1 or IDH2 mutant-positive solid tumors, including glioma, and the other in patients with advanced IDH1 or IDH2 mutant-positive hematologic malignancies whose cancer has progressed on a prior IDH inhibitor therapy. The goal of these trials is to evaluate the safety, pharmacokinetics, pharmacodynamics and clinical activity of AG-881 in advanced solid tumors and hematologic malignancies, respectively.

### ***AG-348: lead PKR activator***

AG-348 is an orally available small molecule and a potent activator of the wild-type (normal) and mutated PKR enzyme, which has resulted in restoration of adenosine triphosphate, or ATP, levels and a decrease in 2,3-diphosphoglycerate, or 2,3-DPG, levels in blood sampled from patients with PK deficiency and treated ex-vivo with AG-348. The wild-type PKR activity of AG-348 allowed 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. On March 24, 2015, the FDA granted us orphan drug designation for AG-348 for treatment of patients with PK deficiency. In December 2016, we announced our decision to advance AG-348 into pivotal development for PK deficiency.

We are evaluating AG-348 in DRIVE PK, a global phase 2, first-in-patient, open-label safety and efficacy clinical trial of AG-348 in adult, transfusion-independent patients with PK deficiency.

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

### ***AG-519***

AG-519 is an orally available small molecule and is a potent activator of the PKR enzyme, with comparable biochemical, cellular and in-vivo activity to AG-348, and was developed as our second PKR activator. We were evaluating AG-519 in a placebo-controlled phase 1 integrated single ascending dose and multiple ascending dose clinical trial in healthy volunteers. In December 2016, we announced that we are no longer developing AG-519 and withdrew our IND for AG-519, following a verbal notification of a clinical hold from the FDA.

### ***Other research and platform programs***

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

### ***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 and potential commercialization of our product candidates. 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.

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[Table of Contents](#)

***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 revenue and expenses during the reporting periods. On an ongoing basis, we evaluate our estimates and judgments. 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 FASB 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 the 2010 Agreement, the AG-881 Agreements and the 2016 Agreement.

***Collaboration and License Revenue***

In January 2011, we adopted FASB Accounting Standards Update (ASU) No. 2009-13, *Multiple-Element Revenue Arrangements* (ASU No. 2009-13), which was codified as ASC 605-25, on a prospective basis for all revenue arrangements entered into or materially modified after the adoption date. The 2010 Agreement was entered into prior to January 1, 2011 and we initially applied our prior 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 2010 Agreement. The amendment was determined to be a material modification pursuant to ASU No. 2009-13. As a result of the amendment, we were required to reevaluate the agreement under ASC 605-25, and 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. As required, all new contracts or modifications to existing contracts, including the AG-881 Agreements entered into in April 2015 will be accounted for under ASC 605-25.

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## [Table of Contents](#)

Pursuant to ASC 605-25, 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.

If a deliverable meets both criteria above, it is considered a separate unit of accounting. If a deliverable does not meet both criteria above, it will be evaluated in combination with other deliverables and, if appropriate, aggregated to form one unit of accounting. The arrangement consideration is then allocated to each unit of accounting based on the relative selling price, using the Company's best estimate of selling price of each unit of accounting, if vendor specific objective evidence or third party evidence is not available. The provisions of ASC 605-25, *Multiple-Element Arrangements*, are then applied to each unit of accounting to determine the appropriate revenue recognition.

We recognize revenue for the units of accounting over the term of the related contract or as undelivered items are delivered (proportional performance method), as appropriate. Under the proportional performance method, the consideration allocated to each unit of accounting is recognized as revenue 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 trial approvals and the estimated patient populations.

Reimbursement of research and development costs under our collaboration agreements are 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, the amounts are determinable and collection of the related receivable is reasonably assured.

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.

### *Milestone Revenue*

We apply the provisions of ASC 605-28, *Revenue Recognition—Milestone Method* (ASC 605-28), pursuant to which 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 ASC 605-28, 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.

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## [Table of Contents](#)

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

### ***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. Examples of estimated accrued research and development expenses include fees paid to:

- CROs in connection with clinical studies;
- investigative sites in connection with clinical studies;
- vendors in connection with preclinical development activities; and
- vendors related to product manufacturing, development and distribution of clinical supplies.

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 stock-based awards granted to employees, including employee stock options, restricted stock units, performance-based stock units and participation in the employee stock purchase plan, to be recognized in the consolidated statements of operations based on their grant date fair values. For stock-based awards granted to employees and to members of the board of directors for their services on the board of directors and for participation in employee stock purchase plan, 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 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.

#### *Expected term*

We use 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

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## [Table of Contents](#)

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 stock options, taking into consideration multiple vesting tranches. We utilize this method due to lack of historical data and the plain-vanilla nature of the share-based awards.

### *Volatility*

Since we were privately held through July 2013, we alone do not have the relevant company-specific historical data to support our expected volatility. As such, we use a weighted-average of expected volatility based on the volatilities of a representative group of publicly traded biopharmaceutical companies; this representative group also includes us. For purposes of identifying representative companies, we considered characteristics such as number of product candidates and their 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. We intend to continue to consistently apply this process using similar entities until a sufficient amount of historical information regarding the volatility of our 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.

### *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*

We have never paid, and do not anticipate paying, any cash dividends in the foreseeable future, and therefore use an expected dividend yield of zero in the option-pricing model.

### *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. We use historical data to estimate pre-vesting option forfeitures and record stock-based compensation expense only for those awards that are expected to vest. To the extent that actual forfeitures differ from the estimates, the difference is recorded as a cumulative adjustment in the period the estimates were revised. Stock-based compensation expense recognized in the financial statements is based on awards that are ultimately expected to vest.

Stock-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 505, *Equity*.

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 options and performance-based stock units***

Performance-based vesting criteria for stock options and stock units primarily relate to milestone events specific to our corporate goals, including but not limited to certain preclinical, clinical and regulatory milestones related to our product candidates. Stock-based compensation expense associated with these performance-based stock options and stock units are 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 is either fully recognized or is being recognized over the remaining service period.

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[Table of Contents](#)**Comparison of years ended December 31, 2016 and 2015**

The following table summarizes our results of operations for the years ended December 31, 2016 and 2015, together with the changes in those items in dollars and as a percentage:

(in thousands)	Years ended December 31,		Dollar change	% change
	2016	2015		
Collaboration revenue—related party	\$ 69,892	\$ 59,119	\$ 10,773	18.2%
Operating expenses:				
Research and development (net of \$19,714 and \$25,173 of cost reimbursement from related party for the years ended December 31, 2016 and 2015, respectively)	220,163	141,827	78,336	55.2
General and administrative	50,714	35,992	14,722	40.9
Loss from operations	(200,985)	(118,700)	(82,285)	69.3
Interest income	2,514	968	1,546	159.7
Net loss	\$ (198,471)	\$ (117,732)	\$ (80,739)	68.6%

*Revenue.* In May 2016, we entered into the 2016 Agreement pursuant to which we received a \$200.0 million upfront payment and which required us to reevaluate the 2010 Agreement and AG-881 Agreements together with the 2016 Agreement. In addition, effective August 15, 2016, Celgene and we agreed to terminate the 2010 Agreement as to the ivosidenib (AG-120) program. For the year ended December 31, 2016, we recognized \$69.9 million in revenue, which consists of \$33.6 million related to new deliverables identified under the 2016 Agreement, including \$10.8 million of revenue related to a change in estimate resulting from a reduction in the total level of effort required for a preclinical achievement of a program reaching earlier than planned, and the recognition of a \$25.0 million milestone payment related to a substantial clinical development milestone achieved. No revenue associated with the ivosidenib (AG-120) program was recognized after the execution of the 2016 Agreement.

In April 2015, we entered into the AG-881 Agreements pursuant to which we received additional consideration and which required us to reevaluate the 2010 Agreement together with the AG-881 Agreements. For the year ended December 31, 2015, we recognized \$59.1 million in revenue, which includes \$27.8 million upon delivery of the ex-U.S. license for ivosidenib (AG-120) and U.S. and ex-U.S. licenses for AG-881.

*Research and development expense.* The increase in research and development expenses was primarily attributable to net increases of \$46.5 million in external services and \$31.8 million in internal expenses; both of these increases are inclusive of reimbursement of costs recorded as a reduction of research and development expenses.

## Table of Contents

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

(in thousands)	Years ended December 31,		Dollar Change	% Change
	2016	2015		
IDH2 inhibitor (enasidenib)	\$ 10,912	\$ 17,537	\$ (6,625)	(37.8)%
<i>Enasidenib reduction of R&amp;D expenses</i>	<i>(1,902)</i>	<i>(7,925)</i>	<i>6,023</i>	<i>(76.0)</i>
IDH1 inhibitor (ivosidenib (AG-120))	92,190	61,651	30,539	49.5
<i>Ivosidenib (AG-120) reduction of R&amp;D expenses(1)</i>	<i>(9,873)</i>	<i>(14,210)</i>	<i>4,337</i>	<i>(30.5)</i>
Pan IDH inhibitor (AG-881)	20,482	16,292	4,190	25.7
<i>AG-881 reduction of R&amp;D expenses</i>	<i>(7,939)</i>	<i>(3,038)</i>	<i>(4,901)</i>	<i>161.3</i>
PKR activator (AG-348)	19,104	19,597	(493)	(2.5)
PKR activator (AG-519)(2)	30,563	6,820	23,743	348.1
Other research and platform programs	66,626	45,103	21,523	47.7
Total research and development expenses, net	<u>\$220,163</u>	<u>\$ 141,827</u>	<u>\$ 78,336</u>	<u>55.2%</u>

- (1) Celgene and we agreed to terminate the 2010 Agreement, effective as of August 15, 2016, as to the program directed to the IDH1 target, for which ivosidenib (AG-120) is the lead development candidate. As a result of the termination, we obtained global development and commercial rights to ivosidenib (AG-120) and the IDH1 program and expect to fund all future development and commercialization costs related to the program. For the year ended December 31, 2016, we earned reimbursements of \$10.8 million related to efforts under this program; however, as a result of the 2016 Agreement, this consideration is primarily recognized as collaboration revenue-related party.
- (2) In December 2016, we announced that we are no longer developing our second PKR activator, AG-519, and withdrew our IND for AG-519, following a verbal notification of a clinical hold from the FDA.

The changes in research and development expense depicted in the table were primarily attributable to the following:

- Enasidenib costs decreased as Celgene assumed the primary development responsibility and has borne a majority of the third-party external costs related to two combination studies: (i) a phase 1b open-label clinical trial of enasidenib or ivosidenib (AG-120) in combination with induction and consolidation therapy, and (ii) phase 1/2 frontline combination clinical trial of either enasidenib or ivosidenib (AG-120) in combination with VIDAZA® (azacitidine).

*Enasidenib reduction of research and development expenses decreased as a result of Celgene assuming the primary development responsibilities for enasidenib in the first quarter of 2015. The cost reimbursements only reflect third-party cost reimbursements.*

- Ivosidenib (AG-120) costs increased as a result of: (i) the two combination studies as described above, (ii) the ongoing enrollment in the expansion portion of the phase 1 clinical trial evaluating single agent ivosidenib (AG-120) in patients with IDH1 mutant-positive advanced hematologic malignancies and (iii) enrollment of the drug-to-drug interaction study. However, the majority of the cost increases are due to us funding 100% of the continued development and commercialization costs, subsequent to the August 15, 2016 termination described above, upon which we obtained global development and commercial rights to ivosidenib (AG-120) and the IDH1 program.

*As described above, for the year ended December 31, 2016, we earned reimbursements of \$10.8 million; however, as a result of the 2016 Agreement, this consideration is primarily recognized as collaboration revenue-related party.*

## Table of Contents

- AG-881 costs increased as a result of the ongoing enrollment of two phase 1 multi-center, open-label clinical trials, one in patients with advanced IDH1 or IDH2 mutant-positive solid tumors, including glioma, and the other in patients with advanced IDH1 or IDH2 mutant-positive hematologic malignancies.

*As AG-881 development services progress, the amount recognized as reduction of AG-881 research and development expenses also increases.*

- AG-348 costs did not materially change as we continued conducting DRIVE PK, a global phase 2, first-in-patient, open-label safety and efficacy clinical trial in adult, transfusion-independent patients with PK deficiency.
- AG-519 costs increased due to the initiation of an integrated SAD and MAD placebo-controlled phase 1 clinical trial of AG-519 in healthy volunteers in the first quarter of 2016. However, on December 15, 2016, we announced that we will no longer develop AG-519 and withdrew our IND application following a verbal notification of a clinical hold from the FDA.
- The increase in the costs of other research and platform programs includes activities related to exploratory efforts, target validation and lead optimization for our discovery and follow-on programs and our proprietary metabolomics platform.

*General and administrative expense.* The increase in general and administrative expense was primarily attributable to the following:

- an increase of \$7.0 million in personnel costs related to an increase in our internal headcount of 29% which includes an increase of \$1.7 million in stock-based compensation expense;
- an increase of \$1.1 million in professional service costs and insurance costs; and
- an increase of \$6.6 million in certain operating expenses, including consulting and facility costs.

*Interest income.* The increase in interest income is attributable to higher investment balances driven by our 2016 Agreement and a more diversified investment portfolio, resulting in higher interest earned.

### Comparison of years ended December 31, 2015 and 2014

The following table summarizes our results of operations for the years ended December 31, 2015 and 2014, together with the changes in those items in dollars and as a percentage:

(in thousands)	Years ended December 31,		Dollar change	% change
	2015	2014		
Collaboration revenue—related party	\$ 59,119	\$ 65,358	\$ (6,239)	(9.5)%
Operating expenses:				
Research and development (net of \$25,173 of cost reimbursement from related party for the year ended December 31, 2015)	141,827	100,371	41,456	41.3
General and administrative	35,992	19,120	16,872	88.2
Loss from operations	(118,700)	(54,133)	(64,567)	119.3
Interest income	968	203	765	376.8
Income tax benefit	—	(426)	426	(100.0)
Net loss	\$ (117,732)	\$ (53,504)	\$ (64,228)	120.0%

## Table of Contents

**Revenue.** In July 2014, we amended our 2010 Agreement which resulted in the application of new accounting guidance to the agreement. As a result of the amendment, we were required to evaluate the agreement under the new revenue recognition accounting guidance on a prospective basis, which resulted in additional revenue being recognized. Prior to the July 2014 amendment, arrangement consideration was recognized ratably over the estimated period of performance. Under this new 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 consideration over the best estimate of selling price of undelivered elements, which fundamentally relates to previously delivered elements under the agreement and includes the exclusive global license for development and commercialization of enasidenib and the reimbursement of on-going development costs related to enasidenib 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. For the year ended December 31, 2015, we recognized \$59.1 million in revenue under the new accounting guidance, which includes \$27.8 million upon delivery of the ex-U.S. license for ivosidenib (AG-120) and U.S. and ex-U.S. licenses for AG-881.

**Research and development expense.** The increase in research and development expenses was primarily attributable to net increases of \$8.5 million in external services and \$32.9 million in internal expenses; both of these increases are inclusive of reimbursement of costs recorded as a reduction of research and development expenses.

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

(in thousands)	Years ended December 31,		Dollar Change	% Change
	2015	2014		
IDH2 inhibitor (enasidenib)	\$ 17,537	\$ 23,455	\$ (5,918)	(25.2)%
<i>Enasidenib reduction of R&amp;D expenses(1)</i>	<i>(7,925)</i>	<i>—</i>	<i>(7,925)</i>	<i>NM</i>
IDH1 inhibitor (ivosidenib (AG-120))	61,651	23,603	38,048	161.2
<i>Ivosidenib (AG-120) reduction of R&amp;D expenses(1)</i>	<i>(14,210)</i>	<i>—</i>	<i>(14,210)</i>	<i>NM</i>
Pan IDH inhibitor (AG-881)	16,292	9,136	7,156	78.3
<i>AG-881 reduction of R&amp;D expenses(1)</i>	<i>(3,038)</i>	<i>—</i>	<i>(3,038)</i>	<i>NM</i>
PKR activator (AG-348)	19,597	16,075	3,522	21.9
PKR activator (AG-519)(2)	6,820	—	6,820	NM
Other research and platform programs	45,103	28,102	17,001	60.5
Total research and development expenses, net	<u>\$ 141,827</u>	<u>\$ 100,371</u>	<u>\$ 41,456</u>	<u>41.3%</u>

- (1) We did not recognize any cost reimbursements as a reduction of research and development expenses during the year ended December 31, 2014.
- (2) Research and development expenses related to AG-519 were not tracked separately by us until 2015. AG-519 research and development expenses incurred in the year ended December 31, 2014 are included within other research and platform programs. In December 2016, we announced that we are no longer developing our second PKR activator, AG-519, and withdrew our IND for AG-519, following a verbal notification of a clinical hold from the FDA.

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## [Table of Contents](#)

The changes in research and development expense depicted in the table were primarily attributable to the following:

- Enasidenib costs decreased as Celgene assumed the primary development responsibilities and began bearing the majority of the third-party external costs in the first quarter of 2015.  
*Upon Celgene's assuming the primary development duties for enasidenib, cost reimbursements related to enasidenib units of accounting are recognized as reduction of research and development expenses. The cost reimbursements are only representative of third-party cost reimbursements.*
- Ivosidenib (AG-120) costs increased as a result of the initiation of two phase 1, multicenter, open-label, dose-escalation and expansion clinical trials for ivosidenib (AG-120), one designed to assess the safety, clinical activity and tolerability of ivosidenib (AG-120) as a single agent in patients with advanced hematologic malignancies and the second designed to evaluate the safety, clinical activity and tolerability of ivosidenib (AG-120) in patients with advanced solid tumors.  
*Effective upon the exercise of the ex-U.S. license in the first quarter of 2015, we became eligible to earn reimbursements related to ivosidenib (AG-120) which were recognized as a reduction of ivosidenib (AG-120) research and development expenses when earned.*
- AG-881 costs increased as a result of the initiation of two phase 1 multi-center, open-label clinical trials, one in patients with advanced IDH1 or IDH2 mutant-positive solid tumors, including glioma, and the other in patients with advanced IDH1 or IDH2 mutant-positive hematologic malignancies.  
*Effective upon the exercise of the U.S. and ex-U.S. licenses for AG-881 and upon the initiation of the AG-881 clinical trials we became eligible to earn reimbursements which were recognized as reduction of AG-881 research and development expenses when earned.*
- AG-348 costs increased as we continued to conduct a phase 1 MAD study in healthy volunteers in 2015.
- AG-519 costs were not tracked separately until the year ended December 31, 2015. The costs for the year ended December 31, 2015 include IND-enabling studies and costs related to the initiation of an integrated SAD and MAD placebo-controlled phase 1 clinical trial of AG-519 in healthy volunteers which began in the first quarter of 2016.
- The increase in the costs of other research and platform programs include activities related to exploratory efforts, target validation and lead optimization for our discovery and follow-on programs and our proprietary metabolomics platform.

*General and administrative expense.* The increase in general and administrative expense was primarily attributable to the following:

- an increase of \$14.1 million in personnel costs related to an increase in our internal headcount of 48% which includes an increase of \$9.7 million in stock-based compensation expense;
- an increase of \$0.4 million in professional service costs and insurance costs; and
- an increase of \$2.4 million in certain operating expenses, including consulting and facility costs.

*Interest income.* The increase in interest income was primarily due to an increase in the average investment balance as a result of our follow-on offering in December 2014 and upfront and contractual reimbursements under our collaboration agreements.

*Income tax benefits.* We did not have a provision for income taxes during 2015 due to our net loss. The benefit for income taxes of \$0.4 million in 2014 was attributable to an abatement received in August 2014 from the Internal Revenue Service of \$0.4 million related to penalties previously paid.

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[Table of Contents](#)

**Liquidity and Capital Resources**

*Sources of liquidity*

Since our inception, and through December 31, 2016, we have funded our operations through upfront, milestone, extension and cost reimbursement payments related to our collaboration agreements, proceeds received from our issuance of preferred stock, our IPO and our follow-on public offerings, including a private placement of common stock to an affiliate of Celgene, which was completed concurrently with our IPO.

In September 2016, we completed a public offering of 3,370,786 shares of our common stock at a public offering price of \$44.50 per share. We received net proceeds from this offering of \$141.0 million, after deducting underwriting discounts and commissions paid by us. In addition, we granted the underwriters the option to purchase up to an additional 505,617 shares of our common stock which option was exercised in September 2016 resulting in additional net proceeds to us of \$21.1 million, after deducting underwriting discounts and commissions paid by us.

In addition to our existing cash, cash equivalents and marketable securities, we are eligible to earn a significant amount of milestone payments, designation fees, license option fees and extension fees and we are entitled to cost reimbursements under our collaboration agreements. 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 agreements 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, 2016, 2015 and 2014:

(in thousands)	Years ended December 31,		
	2016	2015	2014
Net cash provided by (used in) operating activities	\$ 38,562	\$ (76,949)	\$ (59,353)
Net cash (used in) provided by investing activities	(119,350)	128,309	(333,336)
Net cash provided by financing activities	169,778	6,373	335,160
Net increase (decrease) in cash and cash equivalents	<u>\$ 88,990</u>	<u>\$ 57,733</u>	<u>\$ (57,529)</u>

*Net cash used in operating activities.* During the year ended December 31, 2016, we received a \$200.0 million upfront payment related to our 2016 Agreement, \$33.2 million in cost reimbursements related to our collaboration agreements, a \$25.0 million milestone payment in conjunction with the achievement of a substantive development milestone under the 2010 Agreement and \$4.4 million as reimbursement of tenant improvements under our lease agreement. These amounts were offset by increased operating expenses related to increases in clinical study costs due to advancements in our most advanced product candidates, expanded facilities and increased staffing needs due to our expanding operations.

During the year ended December 31, 2015, we received \$34.7 million in cost reimbursements related to our collaboration agreements, \$20.0 million related to Celgene's December 2014 election to extend the discovery phase of the 2010 Agreement and a \$10.0 million upfront payment from our AG-881 Agreements. In addition, we received \$3.8 million of refundable income taxes during the year ended December 31, 2015, related to a previously filed carryback claim. These amounts were offset by increased operating expenses related to increases in clinical study costs due to advancements in our most advanced product candidates, expanded facilities and increased staffing needs due to our expanding operations.

During the year ended December 31, 2014, we received \$40.1 million in cost reimbursements related to our collaboration agreement. In addition, in January 2014, we paid \$6.0 million as payment in full of our U.S.

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## [Table of Contents](#)

federal income tax liability related to the year ended December 31, 2011, including \$1.5 million of interest and penalties accrued. These amounts were offset by increased operating expenses related to increases in clinical study costs due to advancements in our most advanced product candidates, expanded facilities and increased staffing needs due to our expanding operations as well as a \$6.0 million payment 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.

*Net cash provided by (used in) investing activities.* The cash used in investing activities for the year ended December 31, 2016 was primarily the result of higher purchases of marketable securities than proceeds from maturities and sales of marketable securities in addition to \$9.9 million for purchases of property and equipment.

The cash provided by investing activities for the year ended December 31, 2015 was primarily the result of higher proceeds from maturities and sales of marketable securities than purchases of marketable securities offset by \$20.2 million in purchases of property and equipment.

The cash used in investing activities for the year ended December 31, 2014 was primarily the result of higher purchases of marketable securities than proceeds from maturities and sales of marketable securities in addition to \$2.2 million for purchases of property and equipment.

*Net cash provided by financing activities.* The cash provided by financing activities for the year ended December 31, 2016 was primarily the result of proceeds of \$162.1 million from the September 2016 follow-on public offering of our common stock, net of underwriting discounts and commissions, and proceeds of \$7.8 million received from stock option exercises and from stock purchases made pursuant to our employee stock purchase plan. The cash provided by financing activities for the year ended December 31, 2015 was the result of proceeds received from stock option exercises and proceeds received from stock purchases made pursuant to our employee stock purchase plan of \$6.6 million. The cash provided by financing activities for the year ended December 31, 2014 was primarily the result of proceeds of \$333.6 million from our April 2014 and December 2014 follow-on public offerings of our common stock, net of underwriting discounts and commissions, and proceeds received from stock option exercises and proceeds received from stock purchases made pursuant to our employee stock purchase plan of \$2.3 million.

### ***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. 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, 2016, together with anticipated interest income, and anticipated expense reimbursements under our collaboration agreements, but excluding any additional program-specific milestone payments, will enable us to fund our operating expenses and capital expenditure requirements through at least the end of 2018. 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 collaborations;
- the extent to which we acquire or in-license other medicines and technologies;

## [Table of Contents](#)

- the costs, timing and outcome of regulatory review of our product candidates;
- the costs associated with preparation for potential commercial launch for one or more 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. 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 revenue, 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 collaborations. 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, 2016:

(in thousands)	Payments due by period				
	Total	Less than 1 year	1-3 years	3-5 years	More than 5 years
Operating lease obligations(1)	\$51,489	\$ 9,050	\$18,789	\$19,747	\$3,903
Milestone payments(2)	4,600	4,600	—	—	—
License agreements(3)	70	70	—	—	—
Purchase obligations(4)	—	—	—	—	—
<b>Total contractual cash obligations</b>	<b>\$56,159</b>	<b>\$13,720</b>	<b>\$18,789</b>	<b>\$19,747</b>	<b>\$3,903</b>

- (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.

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## [Table of Contents](#)

- (2) As discussed in Note 6 to the consolidated financial statements appearing elsewhere in this Annual Report, we have accrued \$4.6 million in milestone related payments associated with certain agreements,
- (3) 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 totaling \$70,000 per year beginning in 2017. The minimum annual payments are perpetual; however, we have not included license maintenance payments beyond 2017 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.
- (4) 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, 2016, we are obligated to pay up to \$58.9 million to these vendors in future periods, unless terminated.

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 \$3.7 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 25.0% 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.

### **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, 2016, we had cash, cash equivalents and marketable securities of \$573.6 million, consisting primarily of investments in U.S. Treasuries, certificates of deposit and government and corporate debt securities. 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 contract research organizations 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, 2016 and December 31, 2015, 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.

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[Table of Contents](#)

**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, 2016, 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, 2016. 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, 2016, 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.

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[Table of Contents](#)

**Report of Independent Registered Public Accounting Firm**

The Board of Directors and Stockholders  
Agios Pharmaceuticals, Inc.

We have audited Agios Pharmaceuticals, Inc.'s internal control over financial reporting as of December 31, 2016, based on criteria established in the Internal Control–Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (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 exists, 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, 2016, 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, 2016 and 2015, and the related consolidated statements of operations, comprehensive loss, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2016 and our report dated February 16, 2017 expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

Boston, Massachusetts  
February 16, 2017

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[Table of Contents](#)

**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, 2016 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 2017 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 2017 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 2017 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 2017 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 2017 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-40 attached hereto and are filed as part of this Annual Report on Form 10-K.

<a href="#">Report of Independent Registered Public Accounting Firm</a>	F-2
<a href="#">Consolidated Balance Sheets</a>	F-3
<a href="#">Consolidated Statements of Operations</a>	F-4
<a href="#">Consolidated Statements of Comprehensive Loss</a>	F-5
<a href="#">Consolidated Statements Stockholders' Equity</a>	F-6
<a href="#">Consolidated Statements of Cash Flows</a>	F-7
<a href="#">Notes to Consolidated Financial Statements</a>	F-8

**(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.

**Item 16. Form 10-K Summary**

Not applicable.

[Table of Contents](#)

**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 16, 2017

By: /s/ David P. Schenkein

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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.

<u>Signature</u>	<u>Title</u>	<u>Date</u>
<u>/s/ David P. Schenkein</u> David P. Schenkein, M.D.	President, Chief Executive Officer and Director (Principal executive officer)	Date: February 16, 2017
<u>/s/ Andrew Hirsch</u> Andrew Hirsch	Chief Financial Officer (Principal financial officer)	Date: February 16, 2017
<u>/s/ Carman Alenson</u> Carman Alenson	Vice President of Accounting, Treasury and Tax (Principal accounting officer)	Date: February 16, 2017
<u>/s/ Lewis C. Cantley</u> Lewis C. Cantley, Ph.D.	Director	Date: February 16, 2017
<u>/s/ Paul J. Clancy</u> Paul J. Clancy	Director	Date: February 16, 2017
<u>/s/ Ian Clark</u> Ian Clark	Director	Date: February 16, 2017
<u>/s/ Kaye Foster</u> Kaye Foster	Director	Date: February 16, 2017
<u>/s/ Maykin Ho</u> Maykin Ho, Ph.D.	Director	Date: February 16, 2017
<u>/s/ John M. Maraganore</u> John M. Maraganore, Ph.D.	Director	Date: February 16, 2017
<u>/s/ Robert T. Nelsen</u> Robert T. Nelsen	Director	Date: February 16, 2017

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[Table of Contents](#)

Agios Pharmaceuticals, Inc.  
Index to Consolidated Financial Statements

<a href="#">Report of Independent Registered Public Accounting Firm</a>	F-2
<a href="#">Consolidated Balance Sheets</a>	F-3
<a href="#">Consolidated Statements of Operations</a>	F-4
<a href="#">Consolidated Statements of Comprehensive Loss</a>	F-5
<a href="#">Consolidated Statements of Stockholders' Equity</a>	F-6
<a href="#">Consolidated Statements of Cash Flows</a>	F-7
<a href="#">Notes to Consolidated Financial Statements</a>	F-8

---

[Table of Contents](#)

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. as of December 31, 2016 and 2015, and the related consolidated statements of operations, comprehensive loss, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2016. 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, 2016 and 2015, and the consolidated results of their operations and their cash flows for each of the three years in the period ended December 31, 2016, 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, 2016, based on criteria established in the Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 16, 2017 expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

Boston, Massachusetts  
February 16, 2017

[Table of Contents](#)

Agius Pharmaceuticals, Inc.  
Consolidated Balance Sheets  
(In thousands, except share and per share data)

	<b>December 31,</b>	
	<b>2016</b>	<b>2015</b>
<b>Assets</b>		
Current assets:		
Cash and cash equivalents	\$ 160,754	\$ 71,764
Marketable securities	380,560	245,238
Collaboration receivable – related party	4,886	8,225
Tenant improvement and other receivables	3,428	3,374
Prepaid expenses and other current assets	10,264	8,728
Total current assets	559,892	337,329
Marketable securities	32,250	58,905
Property and equipment, net	25,337	23,220
Other non-current assets	1,615	611
Total assets	<u>\$ 619,094</u>	<u>\$ 420,065</u>
<b>Liabilities and stockholders' equity</b>		
Current liabilities:		
Accounts payable	\$ 17,106	\$ 14,748
Accrued expenses	32,002	15,996
Deferred revenue – related party	35,913	19,665
Deferred rent	3,412	2,479
Total current liabilities	88,433	52,888
Deferred revenue, net of current portion – related party	154,297	4,699
Deferred rent, net of current portion	17,773	17,360
Commitments and contingencies ( <i>Note 6</i> )		
Stockholders' equity:		
Preferred stock, \$0.001 par value; 25,000,000 shares authorized, no shares issued and outstanding at December 31, 2016 and 2015	—	—
Common stock, \$0.001 par value; 125,000,000 shares authorized and 42,220,444 and 37,696,502 shares issued and outstanding at December 31, 2016 and 2015, respectively	42	38
Additional paid-in capital	842,013	630,078
Accumulated other comprehensive loss	(313)	(318)
Accumulated deficit	(483,151)	(284,680)
Total stockholders' equity	358,591	345,118
Total liabilities and stockholders' equity	<u>\$ 619,094</u>	<u>\$ 420,065</u>

*See accompanying Notes to Consolidated Financial Statements.*

[Table of Contents](#)

Agius Pharmaceuticals, Inc.  
Consolidated Statements of Operations  
(in thousands, except share and per share data)

	Years Ended December 31,		
	2016	2015	2014
Collaboration revenue – related party	\$ 69,892	\$ 59,119	\$ 65,358
Operating expenses:			
Research and development (net of \$19,714 and \$25,173 of cost reimbursement from related party for the years ended December 31, 2016 and 2015, respectively)	220,163	141,827	100,371
General and administrative	50,714	35,992	19,120
Total operating expenses	<u>270,877</u>	<u>177,819</u>	<u>119,491</u>
Loss from operations	(200,985)	(118,700)	(54,133)
Interest income	2,514	968	203
Loss before income taxes	(198,471)	(117,732)	(53,930)
Benefit from income taxes	—	—	(426)
Net loss	<u>\$ (198,471)</u>	<u>\$ (117,732)</u>	<u>\$ (53,504)</u>
Net loss per share – basic and diluted	<u>\$ (5.07)</u>	<u>\$ (3.15)</u>	<u>\$ (1.59)</u>
Weighted-average number of common shares used in net loss per share – basic and diluted	<u>39,126,400</u>	<u>37,429,262</u>	<u>33,667,024</u>

*See accompanying Notes to Consolidated Financial Statements.*

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[Table of Contents](#)

Agios Pharmaceuticals, Inc.  
Consolidated Statements of Comprehensive Loss  
(in thousands)

	Years Ended December 31,		
	2016	2015	2014
Net loss	\$ (198,471)	\$ (117,732)	\$ (53,504)
Other comprehensive income (loss):			
Unrealized gain (loss) on available-for-sale securities	5	(261)	(71)
Comprehensive loss	<u>\$ (198,466)</u>	<u>\$ (117,993)</u>	<u>\$ (53,575)</u>

*See accompanying Notes to Consolidated Financial Statements.*

[Table of Contents](#)

Agius Pharmaceuticals, Inc.  
Consolidated Statements of Stockholders' Equity  
(in thousands, except share amounts)

	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Stockholders' (Deficit) Equity
	Shares	Amount				
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
Unrealized loss on marketable securities	—	—	—	(261)	—	(261)
Net loss	—	—	—	—	(117,732)	(117,732)
Stock-based compensation expense	—	—	31,574	—	—	31,574
Vesting of restricted stock	8,522	—	6	—	—	6
Issuances costs of follow-on offering from 2014	—	—	29	—	—	29
Issuance of common stock upon exercise of stock options and employee stock purchase plan and vesting of restricted stock units	587,467	1	7,135	—	—	7,136
Balance at December 31, 2015	37,696,502	\$ 38	\$ 630,078	\$ (318)	\$ (284,680)	\$ 345,118
Unrealized gain on marketable securities	—	—	—	5	—	5
Net loss	—	—	—	—	(198,471)	(198,471)
Stock-based compensation expense	—	—	42,086	—	—	42,086
Issuances of common stock upon exercise of stock options and employee stock purchase plan and vesting of restricted stock units	647,539	—	7,703	—	—	7,703
Issuance of common stock for follow-on offering	3,876,403	4	162,146	—	—	162,150
Balance at December 31, 2016	<u>42,220,444</u>	<u>\$ 42</u>	<u>\$ 842,013</u>	<u>\$ (313)</u>	<u>\$ (483,151)</u>	<u>\$ 358,591</u>

*See accompanying Notes to Consolidated Financial Statements.*

[Table of Contents](#)

Agius Pharmaceuticals, Inc.  
Consolidated Statements of Cash Flows  
(in thousands)

	Years Ended December 31,		
	2016	2015	2014
<b>Operating activities</b>			
Net loss	\$(198,471)	\$ (117,732)	\$ (53,504)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:			
Depreciation	5,708	3,342	1,367
Net loss on disposal of fixed assets	—	33	—
Stock-based compensation expense	42,086	31,963	11,506
Net amortization of premiums and discounts on marketable securities	773	539	538
Changes in operating assets and liabilities:			
Collaboration receivable – related party	3,339	(1,733)	(6,016)
Tenant improvement and other receivables	275	(1,040)	(2,334)
Prepaid expenses and other current and non-current assets	(2,695)	(3,768)	(2,878)
Accounts payable	3,501	4,215	7,577
Accrued expenses	16,854	1,633	5,231
Deferred rent	1,346	15,805	3,691
Refundable income taxes and income taxes payable	—	3,841	(5,303)
Deferred revenue – related party	165,846	(14,047)	(19,228)
Net cash provided by (used in) operating activities	<u>38,562</u>	<u>(76,949)</u>	<u>(59,353)</u>
<b>Investing activities</b>			
Purchases of marketable securities	(506,067)	(353,177)	(837,219)
Proceeds from maturities and sales of marketable securities	396,632	501,650	505,528
Purchases of property and equipment	(9,915)	(20,164)	(2,216)
Release of restricted cash	—	—	571
Net cash (used in) provided by investing activities	<u>(119,350)</u>	<u>128,309</u>	<u>(333,336)</u>
<b>Financing activities</b>			
Proceeds from public offering of common stock, net of commissions	162,150	—	333,577
Payment of public offering costs	(230)	(207)	(720)
Net proceeds from stock option exercises and employee stock purchase plan and vesting of restricted stock units	7,858	6,580	2,303
Net cash provided by financing activities	<u>169,778</u>	<u>6,373</u>	<u>335,160</u>
Net increase (decrease) in cash and cash equivalents	88,990	57,733	(57,529)
Cash and cash equivalents at beginning of the period	71,764	14,031	71,560
Cash and cash equivalents at end of the period	<u>\$ 160,754</u>	<u>\$ 71,764</u>	<u>\$ 14,031</u>
<b>Supplemental cash flow information</b>			
Cash paid for income taxes	<u>\$ —</u>	<u>\$ —</u>	<u>\$ 5,980</u>
<b>Supplemental disclosure of non-cash investing and financing transactions:</b>			
Vesting of restricted stock	<u>\$ —</u>	<u>\$ 6</u>	<u>\$ 9</u>
Additions to property, plant and equipment included in accounts payable and accrued expenses	<u>\$ 73</u>	<u>\$ 2,163</u>	<u>\$ 2,118</u>
Proceeds from stock option exercises in other current assets	<u>\$ 32</u>	<u>\$ 186</u>	<u>\$ 20</u>
Public offering costs in other current assets, net of amounts in accounts payable and accrued expenses	<u>\$ 230</u>	<u>\$ —</u>	<u>\$ 236</u>

*See accompanying Notes to Consolidated Financial Statements.*

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements

**1. Nature of Business**

Agius Pharmaceuticals, Inc. (“Agius” or the “Company”) is a biopharmaceutical company committed to the fundamental transformation of patients’ lives through scientific leadership in the field of cancer and rare genetic metabolic disorders. 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. Agius’ therapeutic areas of focus are cancer and rare genetic metabolic disorders, 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 as a platform to create transformative therapies. The Company is located in Cambridge, Massachusetts.

***Liquidity***

The Company has an accumulated deficit as of December 31, 2016 of \$483.2 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.

In September 2016, the Company completed a public offering of 3,370,786 shares of its common stock at a public offering price of \$44.50 per share. The Company received net proceeds from this offering of \$141.0 million, after deducting underwriting discounts and commissions paid by the Company. In addition, the Company granted the underwriters the option to purchase up to an additional 505,617 shares of its common stock which option was exercised in September 2016 resulting in additional net proceeds to the Company of \$21.1 million, after deducting 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 and is entitled to additional cost reimbursements under its collaboration agreements with Celgene Corporation and related subsidiaries (“Celgene”). At December 31, 2016, the Company believes its cash, cash equivalents and marketable securities, totaling \$573.6 million, are sufficient to fund operations for a period of at least one year from the issuance date of the financial statements.

**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 subsidiaries, Agios Securities Corporation and Agios International Sarl. 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.

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

**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.

*Collaboration Agreements with Celgene*

To date, the Company's revenue has primarily been generated from its collaboration agreements with Celgene, a related party through ownership of the Company's common stock, (collectively, "Collaboration Agreements"). In April 2010, the Company entered into a collaboration agreement focused on cancer metabolism. The agreement was amended in October 2011 and July 2014 (the agreement together with the amendments, the "2010 Agreement"). On April 27, 2015, the Company entered into a joint worldwide development and profit share collaboration and license agreements (collectively, the "AG-881 Agreements"). The AG-881 Agreements establish a worldwide collaboration focused on the development and commercialization of AG-881 products. In May 17, 2016, the Company entered into a master research and collaboration agreement (the "2016 Agreement"). The 2016 Agreement establishes a global collaboration focused on the research and development of immunotherapies against certain metabolic targets that exert their antitumor efficacy primarily via the immune system.

*Collaboration and license revenue*

In January 2011, the Company adopted FASB Accounting Standards Update ("ASU") No. 2009-13, *Multiple-Element Revenue Arrangements* ("ASU 2009-13"), which was codified within ASC 605-25, on a prospective basis for all revenue arrangements entered into or materially modified after the adoption date. The 2010 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 2010 Agreement. The amendment was determined to be a material modification pursuant to ASU 2009-13. As a result of the amendment, the Company was required to reevaluate the agreement under ASC 605-25, and began recognizing revenue for the arrangement under this guidance on a prospective basis, as discussed further in Note 3. As required, all new contracts or modifications to existing contracts, including the AG-881 Agreements and the 2016 Agreement discussed further in Note 3, have been accounted for under ASC 605-25.

Pursuant to ASC 605-25, 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.

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

If a deliverable meets both criteria above, it is considered a separate unit of accounting. If a deliverable does not meet both criteria above, it will be evaluated in combination with other deliverables and, if appropriate, aggregated to form one unit of accounting. The arrangement consideration is then allocated to each unit of accounting based on the relative selling price, using the Company's best estimate of selling price of each unit of accounting, if vendor specific objective evidence or third party evidence is not available. The provisions of ASC 605-25 are then applied to each unit of accounting to determine the appropriate revenue recognition.

The Company recognizes revenue for the units of accounting over the term of the related contract or as undelivered items are delivered (proportional performance method), as appropriate. Under the proportional performance method, the consideration allocated to each unit of accounting is recognized as revenue 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 trial approvals and the estimated patient populations.

Reimbursement of research and development costs under the Company's Collaboration Agreements are 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.

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.

*Milestone revenue*

The Company applies the provisions of ASC 605-28, *Revenue Recognition – Milestone Method* pursuant to which 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 ASC 605-28, 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.

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

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

***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 718, *Compensation – Stock Compensation*. ASC 718 requires all stock-based awards granted to employees, including employee stock options, restricted stock units, performance-based stock units and participation in the employee stock purchase plan, to be recognized in the consolidated statements of operations based on their grant date fair values. For stock-based awards granted to employees and to members of the board of directors for their services on the board of directors and for participation in employee stock purchase plan, 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.

Stock-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 505, *Equity*. For equity instruments granted to non-employees, the Company recognizes stock-based compensation expense using an accelerated recognition method.

***Income taxes***

Income taxes are recorded in accordance with ASC 740, *Accounting for Income Taxes*, 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. The Company evaluated whether any uncertain tax positions arise from commencing operations of its wholly owned subsidiary, Agius International Sarl, and determined no uncertain tax positions existed. As of December 31, 2016 and 2015, the Company does not have any uncertain tax positions.

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

**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, 2016 and 2015.

**Cash and cash equivalents**

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

**Marketable securities**

Marketable securities at December 31, 2016 and 2015 consisted primarily of investments in certificates of deposits, United States Treasuries, government securities and corporate debt securities. 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. 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, 2016 and 2014. There were immaterial realized gains on marketable securities for the year ended December 31, 2015.

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, 2016 consisted of the following (in thousands):

	<u>Amortized Cost</u>	<u>Unrealized Gains</u>	<u>Unrealized Losses</u>	<u>Fair Value</u>
Current:				
Certificates of deposit	\$ 11,280	\$ 2	\$ (3)	\$ 11,279
U.S. Treasuries	141,678	2	(62)	141,618
Government securities	19,533	—	(23)	19,510
Corporate debt securities	208,285	3	(135)	208,153
Non-current:				
Certificates of deposit	7,600	6	(13)	7,593
Government securities	4,499	—	(21)	4,478
Corporate debt securities	20,248	—	(69)	20,179
	<u>\$ 413,123</u>	<u>\$ 13</u>	<u>\$ (326)</u>	<u>\$ 412,810</u>

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[Table of Contents](#)Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

Marketable securities at December 31, 2015 consisted of the following (in thousands):

	<u>Amortized Cost</u>	<u>Unrealized Gains</u>	<u>Unrealized Losses</u>	<u>Fair Value</u>
Current:				
Certificates of deposit	\$ 11,248	\$ —	\$ (5)	\$ 11,243
U.S. Treasuries	234,130	10	(145)	233,995
Non-current:				
U.S. Treasuries	59,083	—	(178)	58,905
	<u>\$ 304,461</u>	<u>\$ 10</u>	<u>\$ (328)</u>	<u>\$ 304,143</u>

At December 31, 2016 and 2015, 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, 2016 and 2015, the Company held 158 and 74 debt securities, respectively, that were in an unrealized loss position. The aggregate fair value of debt securities in an unrealized loss position at December 31, 2016 and 2015 was \$335.4 million and \$207.4 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, 2016 and 2015. 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, 2016 and 2015.

**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 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.

[Table of Contents](#)

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

*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, 2016 (in thousands):

	<u>Level 1</u>	<u>Level 2</u>	<u>Level 3</u>	<u>Total</u>
Cash equivalents	\$ 143,352	\$ 7,897	\$ —	\$ 151,249
Marketable securities:				
Certificates of deposit	—	18,872	—	18,872
U.S. Treasuries	141,618	—	—	141,618
Government securities	11,514	12,474	—	23,988
Corporate debt securities	—	228,332	—	228,332
	<u>\$ 296,484</u>	<u>\$ 267,575</u>	<u>\$ —</u>	<u>\$ 564,059</u>

The following table summarizes the cash equivalents and marketable securities measured at fair value on a recurring basis as of December 31, 2015 (in thousands):

	<u>Level 1</u>	<u>Level 2</u>	<u>Level 3</u>	<u>Total</u>
Cash equivalents	\$ 59,332	\$ —	\$ —	\$ 59,332
Marketable securities:				
Certificates of deposit	—	11,243	—	11,243
U.S. Treasuries	292,900	—	—	292,900
	<u>\$ 352,232</u>	<u>\$ 11,243</u>	<u>\$ —</u>	<u>\$ 363,475</u>

Cash equivalents and marketable securities have been initially valued at the transaction price and subsequently revalued, 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. 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, 2016 or 2015.

There have been no changes to the valuation methods during the years ended December 31, 2016 and 2015. The Company evaluates transfers between levels at the end of each reporting period. Due to the lack of an active market, the Company transferred \$11.0 million of government securities from Level 1 to Level 2 during the year ended December 31, 2016. There were no transfers of assets or liabilities between Level 1 and Level 2 during the year ended December 31, 2015. The Company had no financial assets or liabilities that were classified as Level 3 at any point during the years ended December 31, 2016 and 2015.

Due to their short-term nature, the carrying amounts reflected in the consolidated balance sheets for cash, collaboration receivable – related party, tenant improvement and other receivables, prepaid expenses and other current and non-current assets, accounts payable, and accrued expenses approximate their fair values at December 31, 2016 and 2015.

Agios Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

***Collaboration and other receivables***

Collaboration receivables as of December 31, 2016 and 2015 represent amounts due under our Collaboration Agreements for reimbursements of certain costs. 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, 2016 and 2015, 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 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, 2016.

***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 operating decision maker view the Company's operations and manage its business as one operating segment.

***Net loss per share***

Basic net loss per share is calculated by dividing net loss by the weighted-average shares outstanding during the period, without consideration for common stock equivalents. Diluted net loss per share is calculated by adjusting

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

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 calculation, stock options, including performance-based stock options which were determined to be probable of achievement, restricted stock units, unvested restricted stock and employee stock purchase plan shares are considered to be common stock equivalents but are excluded from the calculation of diluted net loss per share as their effect would be anti-dilutive.

Since the Company had a net loss for all periods presented, the effect of all potentially dilutive securities is anti-dilutive. Accordingly, basic and diluted net loss per share was the same for the years ended December 31, 2016, 2015 and 2014. Furthermore, 323,339 performance-based stock options and stock units that were previously granted had not vested as of December 31, 2016 and were excluded from diluted shares outstanding as the vesting conditions for the awards, discussed further in Note 8 “Share-Based Payments,” had not been met as of December 31, 2016.

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,		
	2016	2015	2014
Stock options	5,218,880	4,618,697	3,795,420
Restricted stock units	77,050	15,000	10,000
Unvested restricted stock	—	—	8,522
Employee stock purchase plan shares	24,018	7,721	7,159
	<u>5,319,948</u>	<u>4,641,418</u>	<u>3,821,101</u>

#### **Recent accounting pronouncements**

##### *Revenue from Contracts with Customers*

In May 2014, the FASB issued ASU No. 2014-09, *Revenue from Contracts with Customers (Topic 606)* (“ASU 2014-09”). Subsequently, the FASB also issued ASU 2015-14, *Revenue from Contracts with Customers (Topic 606)*, which adjusted the effective date of ASU 2014-09; ASU No. 2016-08, *Revenue from Contracts with Customers (Topic 606): Principal versus Agent Considerations (Reporting Revenue Gross versus Net)*, which amends the principal-versus-agent implementation guidance and illustrations in ASU 2014-09; ASU No. 2016-10, *Revenue from Contracts with Customers (Topic 606): Identifying Performance Obligations and Licensing*, which clarifies identifying performance obligation and licensing implementation guidance and illustrations in ASU 2014-09; and ASU No. 2016-12, *Revenue from Contracts with Customers (Topic 606): Narrow-Scope Improvements and Practical Expedients*, which addresses implementation issues and is intended to reduce the cost and complexity of applying the new revenue standard in ASU 2014-09 (collectively, the “Revenue ASUs”).

The Revenue ASUs provide an accounting standard 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, 2017, with an option to early adopt for interim and annual periods beginning after December 15, 2016. The guidance permits two methods of adoption: retrospectively to each prior reporting period presented (the full retrospective method), or retrospectively with the cumulative effect of initially applying the guidance recognized at the date of initial

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

application (the modified retrospective method). We currently anticipate adoption of the new standard effective January 1, 2018 under the modified retrospective method. The Company is in the process of determining the impact of the Revenue ASUs on its financial statements; however, the adoption of the Revenue ASUs is expected to have a significant impact on the Company's notes to consolidated financial statements and its internal controls over financial reporting.

*Other Recent Accounting Pronouncements*

In October, 2016, the FASB issued ASU No. 2016-16, *Income Taxes (Topic 740): Intra-Entity Transfers of Assets Other Than Inventory* ("ASU 2016-16"), which removes the prohibition in ASC 740 against the immediate recognition of the current and deferred income tax effects of intra-entity transfers of assets other than inventory. ASU 2016-16 is effective for the Company for annual periods beginning after December 15, 2017, and interim periods within those annual periods. Early adoption is permitted as of the beginning of a fiscal year for which neither the annual nor the interim (if applicable) financial statements have been issued. The Company is currently in the process of evaluating the impact of the guidance on its consolidated financial statements.

In March 2016, the FASB issued ASU No. 2016-09, *Compensation – Stock Compensation (Topic 718): Improvements to Employee Share-Based Payment Accounting* ("ASU 2016-09"), which simplifies several aspects of the accounting for employee share-based payment transactions, including income taxes consequences, classification of awards as either equity or liabilities, and classification in the statement of cash flows. ASU 2016-09 is effective for annual reporting periods beginning after December 15, 2016, including interim periods within those annual reporting periods. The Company is currently in the process of evaluating the impact of the guidance on its consolidated financial statements.

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842)* ("ASU 2016-02"), which establishes principles that lessees and lessors shall apply to report useful information to users of financial statements about the amount, timing and uncertainty of cash flows arising from a lease. ASU 2016-02 is effective for annual periods beginning after December 15, 2018 and interim periods therein, with early adoption permitted. The Company is currently in the process of 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, for potential recognition or disclosure in its consolidated financial statements. All significant subsequent events have been properly disclosed in the consolidated financial statements.

**3. Celgene Collaboration Agreements**

*2016 Agreement*

On May 17, 2016, Agius entered into the 2016 Agreement, which establishes a global collaboration focused on the research and development of immunotherapies against certain metabolic targets that exert their antitumor efficacy primarily via the immune system. In addition to new programs identified under the 2016 Agreement, both parties have also agreed that all future development and commercialization of two remaining cancer

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

metabolism programs discovered under the 2010 Agreement, including a program focused on methylthioadenosine phosphorylase, or MTAP, deleted cancers, will now be governed by the 2016 Agreement.

During the research term of the 2016 Agreement, the Company plans to conduct research programs focused on discovering compounds that are active against metabolic targets in the immuno-oncology (“IO”) field. The initial four-year research term will expire on May 17, 2020. The research term may be extended for up to two, or in specified cases, up to four additional one-year terms.

For each program under the 2016 Agreement, Agios may nominate compounds that meet specified criteria as development candidates and, in limited circumstances, Celgene may also nominate compounds as development candidates for each such program. Celgene may designate the applicable program for further development following any such nomination, after which the Company may conduct, at the Company’s expense, additional pre-clinical and clinical development for such program through completion of an initial phase 1 dose escalation study.

At the end of the research term, Celgene may designate for continued development up to three research programs for which development candidates have yet to be nominated, which are referred to as continuation programs. Agios may conduct further research and pre-clinical and clinical development activities on any continuation program, at the Company’s expense, through completion of an initial phase 1 dose escalation study.

The Company has granted Celgene the right to obtain exclusive options to development and commercialization rights for each program that Celgene has designated for further development and for each continuation program. Celgene may exercise each such option beginning on the designation of a development candidate for such program (or on the designation of such program as a continuation program) and ending on the earlier of the end of a specified period after Celgene is furnished with specified information about the initial phase 1 dose escalation study for such program, or January 1, 2030. Research programs that have applications in the inflammation or autoimmune (“I&I”) field that may result from the 2016 Agreement will also be subject to the exclusive options described above.

Agios will retain rights to any program that Celgene does not designate for further development or does not exercise its option.

Under the terms of the 2016 Agreement, following Celgene’s exercise of its option with respect to a program, the parties will enter into either a co-development and co-commercialization agreement if such program is in the IO field, or a license agreement if such program is in the I&I field. Under each co-development and co-commercialization agreement, the two parties will co-develop and co-commercialize licensed products worldwide. Either Agios or Celgene will lead development and commercialization of licensed products for the United States and Celgene will lead development and commercialization of licensed products outside of the United States. Depending on the country, the parties will each have the right to provide a portion of field-based marketing activities. Under each license agreement, Celgene will have the sole right to develop and commercialize licensed products worldwide.

*Co-development and co-commercialization agreements*

Under each co-development and co-commercialization agreement entered into under the 2016 Agreement, the parties will split all post-option-exercise worldwide development costs, subject to specified exceptions, as well as any profits from any net sales of, or commercialization losses related to, licensed products in the IO field. Celgene has the option to designate one program in the IO field as the 65/35 program, for which Celgene will be the lead party for the United States and will have a 65% profit or loss share. For programs in the IO field other

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

than the 65/35 program, the Company and Celgene will alternate, on a program-by-program basis, being the lead party for the United States, with Agios having the right to be the lead party for the first such program, and each will have a 50% profit or loss share. The lead party for the United States will book commercial sales of licensed products, if any, in the United States, and Celgene will book commercial sales of licensed products, if any, outside of the United States.

*License agreements*

Under each license agreement under the 2016 Agreement, Celgene will be responsible for all post-option-exercise worldwide development and associated costs, subject to specified exceptions, as well as worldwide commercialization and associated costs, for licensed products.

*Financial terms*

Under the terms of the 2016 Agreement, the Company received an initial upfront payment in the amount of \$200.0 million. The 2016 Agreement provides specified rights to extend the research term for up to two, or in specified cases, up to four, additional years by paying a \$40.0 million per-year extension fee. Celgene will pay an \$8.0 million designation fee for each program that Celgene designates for further development and for each continuation program. For each program as to which Celgene exercises its option to develop and commercialize, subject to antitrust clearance, Celgene will pay an option exercise fee of at least \$30.0 million for any designated development program and at least \$35.0 million for any continuation programs. In certain cases, Celgene may exercise its option to develop and commercialize two early-stage I&I programs, prior to Celgene designating the program for further development, by paying an option exercise fee of \$10.0 million.

For the co-development and co-commercialization program Celgene designates the 65/35 program in the IO field, the Company is eligible to receive up to \$208.8 million in potential milestone-based payments. The potential milestone-based payments for that program are comprised of: (i) a \$25.0 million milestone-based payment upon achievement of a specified clinical development event and (ii) up to \$183.8 million in milestone-based payments upon achievement of specified regulatory milestone events. For each co-development and co-commercialization program in the IO field other than the 65/35 program, Agios is eligible to receive up to \$168.8 million in potential milestone-based payments. The potential milestone-based payments for such programs are comprised of: (i) a \$20.0 million milestone-based payment upon achievement of a specified clinical development event and (ii) up to \$148.8 million in milestone-based payments upon achievement of specified regulatory milestone events.

For each licensed program in the I&I field, Agios is eligible to receive royalties at tiered, low double-digit percentage rates on Celgene's net sales, if any, of the applicable licensed products and up to \$386.3 million in potential milestone-based payments. The potential milestone-based payments for such programs are comprised of: (i) a \$25.0 million milestone-based payment upon achievement of a specified clinical development event, (ii) up to \$236.3 million in milestone-based payments upon achievement of specified regulatory milestone events, and (iii) up to \$125.0 million in milestone-based payments upon achievement of specified commercial milestone events.

*Opt-out right*

Under the 2016 Agreement, the Company may elect to opt out of the cost and profit share under any co-development and co-commercialization agreement, subject to specified exceptions. Upon opting out, Celgene will have the sole right to develop, manufacture and commercialize the applicable licensed products throughout the world, at its cost, and the Company will undertake transitional activities reasonably necessary to transfer the

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

development, manufacture and commercialization of such licensed products to Celgene, at the Company's expense. Further, in lieu of the profit or loss sharing described above, Agios would be eligible to receive royalties at tiered, low double-digit percentage rates on Celgene's net sales, if any, of the applicable licensed products. However, the Company would continue to be eligible to receive the developmental and regulatory milestone-based payments described above.

*Term*

The term of the 2016 Agreement commenced on May 17, 2016 and, if not terminated earlier, will expire upon later of the last-to-expire of the research term and all option exercise periods, or, if an option is exercised by Celgene for one or more programs in the collaboration, upon the termination or expiration of the last-to-exist co-development and co-commercialization agreement or license agreement, as applicable, for any such program.

*Termination*

Subject to specified exceptions, Celgene may terminate the 2016 Agreement in its entirety for any reason by providing Agios with prior written notice if there are no active co-development and co-commercialization agreements or license agreements in place or on a program-by-program basis if there are no active co-development and co-commercialization agreements or license agreements in place for the terminated program(s). Either party may terminate the 2016 Agreement for the insolvency of the other party. On a program-by-program basis, prior to the exercise of an option, either party may terminate the 2016 Agreement either in its entirety or with respect to one or more programs on prior written notice to the other party in the case of an uncured material breach by the other party that frustrates the fundamental purpose of the 2016 Agreement. Following the exercise of an option for a program, either party may terminate the 2016 Agreement with respect to such program if such party terminates the co-development and co-commercialization agreement or license agreement for such program for an uncured material breach by the other party that frustrates the fundamental purpose of such agreement. Either party may terminate a co-development and co-commercialization agreement or a license agreement upon the bankruptcy or insolvency of the other party. Either party also has the right to terminate the co-development and co-commercialization agreement or license agreement if the other party or any of its affiliates challenges the validity, scope or enforceability of or otherwise opposes, any patent included within the intellectual property rights licensed to the other party under such agreement.

*Exclusivity*

While any of Celgene's options remain available under the 2016 Agreement, subject to specified exceptions, the Company may not directly or indirectly develop, manufacture or commercialize, outside of the 2016 Agreement, any therapeutic modality in the IO field or the I&I field with specified activity against a metabolic target.

During the term of each co-development and co-commercialization agreement and license agreement, subject to specified exceptions, neither the Company nor Celgene may directly or indirectly develop, manufacture or commercialize outside of such agreement any therapeutic modality in any field with specified activity against the metabolic target that is the focus of the program licensed under such agreement.

***AG-120 Letter Agreement***

On May 17, 2016, Agios entered into a letter agreement regarding ivosidenib (AG-120) (the "AG-120 Letter Agreement"). Under the AG-120 Letter Agreement, the parties have agreed to terminate the 2010 Agreement, effective as of August 15, 2016, as to the program directed to the IDH1 target, for which ivosidenib (AG-120) is

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

the lead development candidate. Under the 2010 Agreement, Celgene had held development and commercialization rights to the IDH1 program outside of the United States and Agios held such rights inside the United States. As a result of the AG-120 Letter Agreement, the Company will obtain global rights to ivosidenib (AG-120) and the IDH1 program. Neither party will have any further financial obligation, including royalties or milestone payments, to the other concerning ivosidenib (AG-120) or the IDH1 program. Under the AG-120 Letter Agreement, the parties have also agreed to conduct specified transitional activities in connection with the termination. In addition, pursuant to the AG-120 Letter Agreement, the parties are released from their exclusivity obligations under the 2010 Agreement with respect to the IDH1 program. The AG-120 Letter Agreement does not affect the AG-881 Agreements, which are directed to both the IDH1 target and the IDH2 target.

***AG-881 Agreements***

On April 27, 2015, the Company entered into the AG-881 Agreements. The AG-881 Agreements establish a joint worldwide collaboration focused on the development and commercialization of AG-881 products. Under the terms of the AG-881 Agreements, the Company received an initial upfront payment of \$10.0 million in May 2015 and is eligible to receive milestone-based payments described below. The parties will equally split all worldwide development costs, subject to specified exceptions, as well as any profits from any net sales of, or commercialization losses related to, licensed AG-881 products.

The Company is eligible to receive up to \$70.0 million in potential milestone payments related to AG-881 under the AG-881 Agreements. The potential milestone payments are comprised of: (i) a \$15.0 million milestone payment for filing of first NDA in a major market and (ii) up to \$55.0 million in milestone payments upon achievement of specified regulatory milestone events. The Company may also receive royalties at tiered, low- to mid-teen percentage rates on net sales if Celgene elects to not participate in the development and commercialization of AG-881.

***2010 Agreement and amendments***

In April 2010, the Company entered into the 2010 Agreement. The 2010 Agreement was amended in October 2011 and July 2014. The goal of the collaboration was to discover, develop and commercialize disease-altering therapies in oncology based on the Company's cancer metabolism research platform. The Company initially led discovery, preclinical and early clinical development for all cancer metabolism programs under the collaboration. The discovery phase of the 2010 Agreement expired in April 2016.

Upon agreement to terminate the 2010 Agreement, effective as of August 15, 2016, as to the program directed to the IDH1 target, for which ivosidenib (AG-120) is the lead development candidate, the sole program remaining under the 2010 Agreement is enasidenib, a co-commercialized licensed program for which Celgene funds global development and commercialization activities. The Company has exercised its right to participate in a portion of commercialization activities in the United States for enasidenib in accordance with the applicable commercialization plan.

Under the 2010 Agreement, the Company is eligible to receive up to \$120.0 million in potential milestone payments for the enasidenib program. The potential milestone payments are comprised of: (i) a \$25.0 million milestone payment upon achievement of a specified clinical development milestone event, which was earned upon the initiation of the IDHENTIFY clinical trial, (ii) up to \$70.0 million in milestone payments upon achievement of specified ex-U.S. regulatory milestone events, and (iii) a \$25.0 million milestone payment upon achievement of a specified commercial milestone event.

Under the 2010 Agreement, 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

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

United States. Assuming all other revenue recognition criteria are met, royalty payments will be recognized as revenue in the period in which they are earned. To date, the Company has not earned any royalty payments under the 2010 Agreement.

Unless terminated earlier by either party, the term of the 2010 Agreement will continue until the expiration of all royalty terms with respect to enasidenib. Celgene may terminate this agreement for convenience in its entirety upon ninety days written notice to the Company. If either party is in material breach and fails to cure such breach within the specified cure period, the other party may terminate the 2010 Agreement in its entirety. Either party may terminate the agreement in the event of specified insolvency events involving the other party.

***Accounting analysis and revenue recognition—collaboration revenue***

*Pre-July 2014*

Prior to the July 2014 amendment of the 2010 Agreement, 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 2010 Agreement. Upfront consideration of approximately \$121.2 million 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. 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 recognized the premium as revenue on a straight-line basis over the performance period.

For the period January 1, 2014 through the July 2014 amendment date, the Company recognized a total of \$42.7 million in revenue under the previous accounting guidance and upon the modification.

*July 2014 – April 2015*

The July 2014 amendment of the 2010 Agreement was determined to be a material modification of the 2010 Agreement due to the change in the total potential consideration that was more than insignificant and significant changes to certain of the deliverables in the arrangement. Upon concluding that the 2010 Agreement had been materially modified in July 2014, the Company identified the remaining deliverables under the arrangement and determined its best estimates of selling price for the undelivered elements as of the modification date as vendor specific objective evidence and third-party evidence were not available. 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 arrangement consideration and the best estimate of selling price of the undelivered items was recognized as revenue at the modification date.

The undelivered items from the July 2014 modification, the related best estimate of selling price, the method of recognizing the allocated consideration, and the revenue recognized related to each unit of accounting through April 27, 2015, the effective date of the AG-881 Agreements, was as follows:

- License for the split licensed program—ivosidenib (AG-120): The Company developed the best estimate of selling price of the license by probability weighting multiple cash flow scenarios using the income

Agios Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (continued)

approach. There were significant judgments and estimates inherent in the determination of the best estimate of selling price of this unit of accounting. Should different reasonable assumptions be utilized, the best estimate of selling price and the associated revenue recognized would be different. The Company allocated \$21.2 million to the license which was delivered in January 2015. During the period January 1, 2015 through April 27, 2015, the Company recognized the non-contingent consideration allocated to this unit of accounting of \$15.8 million as collaboration revenue. The Company did not recognize any revenue related to this unit of accounting for the period July 2014 through December 31, 2014.

- Development services for five separate on-going phase 1 clinical trials (each of which is a separate unit of accounting): The Company developed the best estimate of selling price of the on-going phase 1 clinical trial development services of \$50.8 million for all five studies using management's best estimate of the cost of obtaining these services at arm's length from a third-party provider, as well as internal full time equivalent costs to support the development services. The amount allocated to these units of accounting is recognized as revenue on a proportional performance basis as services are provided. As committed to on the date of the July 2014 amendment, the Company has completed services for three of the on-going phase 1 clinical trials and expected services for the remaining two on-going phase 1 clinical trials were expected to be performed through the second quarter of 2016. As additional consideration is earned and allocated to the three fully delivered units of accounting it is recognized immediately. During the period January 1, 2015 through April 27, 2015, and for the period July 2014 through December 31, 2014, the Company recognized the non-contingent consideration allocated to these units of accounting of \$14.7 million and \$17.4 million, respectively, as collaboration revenue.
- 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 at arm's length from a third-party provider. The amount allocated to this unit of accounting was recognized as revenue ratably over the performance period. During the period January 1, 2015 through April 27, 2015 and for the period July 2014 through December 31, 2014, the Company recognized the non-contingent consideration allocated to this unit of accounting of \$5.0 million and \$5.2 million, respectively, as collaboration revenue.
- 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 was recognized as revenue ratably over the performance period. During the period January 1, 2015 through April 27, 2015 and for the period July 2014 through December 31, 2014, the Company recognized the non-contingent consideration allocated to this unit of accounting of \$0.1 million, in each period, as collaboration revenue.

In December 2014, Celgene elected to extend the term of the discovery period over which the Company was providing on-going research and development services from five to six years, to April 2016. As a result of the extension, the Company received a \$20.0 million extension payment in May 2015. The Company evaluated the extension and concluded that upon exercise it is obligated to provide its committee participation and research and development services for a period of one year from April 2015 through April 2016, and as such revenue should be recognized ratably over the performance period of April 2015 to April 2016 as services are rendered. The Company recognized revenue of \$0.7 million related to this substantive option during the period April 16, 2015 through April 27, 2015.

Beginning in the first quarter of 2015, the parties agreed to plans to advance enasidenib into later stage development studies. Pursuant to the terms of the 2010 Agreement, the parties agreed to transition primary

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

development responsibilities for enasidenib to Celgene for later stage development at which point Celgene became the lead development party for enasidenib. During the transition, the Company continued to manage certain arrangements with third-party service providers whose contracts were assigned to Celgene. The Company determined it is no longer the primary obligor of these arrangements and, when considering the other factors included within ASC 605-45, Revenue Recognition—Principal Agent Considerations, determined reimbursement of amounts incurred under third-party contracts should be reported on a net basis within research and development expense. The Company re-assessed its estimate of the total level of effort required to perform the development services related to enasidenib as a result of the contract assignments and recorded a change in estimate during the three months ended March 31, 2015. This change in estimate resulted in the recognition of an additional \$5.1 million of revenue, which is included within revenue related to development services for five separate on-going phase 1 clinical trials discussed earlier within this footnote. Including the \$3.8 million presented as a reduction of research and development expenditures, the change in estimate reduced the Company's net loss by \$8.9 million and caused a decrease in net loss per share of \$0.24 during the three months ended March 31, 2015.

During the period January 1, 2015 through April 27, 2015, the execution date of the AG-881 Agreements, the Company performed planning services on behalf of Celgene related to an expanded phase 1 clinical trial of enasidenib. The Company determined the work represented a substantive option under the 2010 Agreement. The Company also determined it is not the primary obligor of the underlying third-party contracts and determined that reimbursements of amounts incurred under the contracts should be reported on a net basis in research and development expense. Reimbursements of services performed directly by the Company are presented on a gross basis as collaboration revenue. During the period January 1, 2015 through April 27, 2015, the Company recognized \$0.4 million in revenues and recorded \$0.9 million as a reduction in research and development costs related to these services. Costs reimbursed for services performed directly by the Company are presented as collaboration revenues.

*April 2015 – May 2016*

The AG-881 Agreements, executed on April 27, 2015, were determined to be a modification of the 2010 Agreement due to the AG-881 Agreements including a compound originally identified within the 2010 Agreement. As a result of the modification the Company identified the remaining deliverables under the 2010 Agreement and the AG-881 Agreements and determined the 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, the initial payment of \$10.0 million under the AG-881 Agreements and other consideration under the 2010 Agreement and the AG-881 Agreements that was deemed to be determinable at the modification date, to each unit of accounting relative to its best estimate of selling price. 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 at April 27, 2015, and the method of recognizing the allocated consideration, for each unit of accounting are as follows:

- Licenses for the AG-881 program: The Company developed the best estimate of selling price of the U.S. license and the rest of world 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 estimate of the direct cost incurred to generate future cash flows, a discount rate and other business forecast factors. There are significant judgments and estimates inherent in the determination of the best estimate of selling price of these units 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 revenue

Agios Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (continued)

recognized would be different. The Company developed a best estimate of selling price of the licenses of \$33.2 million. The Company recognizes the non-contingent consideration allocated to these units of accounting upon delivery of the licenses, which occurred immediately upon the execution of the AG-881 Agreements. During the period January 1, 2016 through May 17, 2016, the effective date of the 2016 Agreement, the Company recognized the non-contingent consideration allocated to this unit of accounting of \$1.4 million as collaboration revenue. For the period April 27, 2015 through December 31, 2015, the Company recognized the non-contingent consideration allocated to this unit of accounting of \$12.0 million as collaboration revenue.

- Four separate on-going development services for which the Company determined it is acting as the principal of all development activities (each of which is a separate unit of accounting): The Company developed the best estimate of selling price for all four of the on-going development services of \$12.7 million using management's best estimate of the cost of obtaining these services at arm's length 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 expected the services to be performed through 2017. When considering the factors included within ASC 605-45, the Company determined it is the principal of all development activities and is required to present reimbursement of amounts incurred for these services as revenue. During the period January 1, 2016 through May 17, 2016, the Company recognized the non-contingent consideration allocated to these units of accounting of \$1.7 million as collaboration revenue. For the period April 27, 2015 through December 31, 2015, the Company recognized the non-contingent consideration allocated to these units of accounting of \$1.7 million as collaboration revenue.
- Four separate on-going development services for which the Company determined it is not acting as the principal of all development activities (each of which is a separate unit of accounting): The Company developed the best estimate of selling price for all four of the on-going development services of \$97.3 million using management's best estimate of the cost of obtaining these services at arm's length 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 on a proportional performance basis as services are provided. The Company expected the services to be performed through 2017. When considering the factors included within ASC 605-45, the Company determined it is not the principal of all development activities and is required to present reimbursement of amounts incurred for these services on a net basis as a reduction of research and development expenses. During the period January 1, 2016 through May 17, 2016, the Company recognized the non-contingent consideration allocated to these units of accounting of \$7.5 million as a reduction of research and development costs related to these services. For the period April 27, 2015 through December 31, 2015, the Company recognized the non-contingent consideration allocated to these units of accounting of \$17.1 million as a reduction of research and development costs related to these services.
- On-going research and development: The Company developed the best estimate of selling price of the research and development services of \$30.5 million using management's best estimate of the cost of obtaining these services at arm's length from a third-party provider. The amount allocated to this unit of accounting is being recognized as revenue ratably over the performance period through April 2016. During the period January 1, 2016 through May 17, 2016, the Company recognized the non-contingent consideration allocated to this unit of accounting of \$4.6 million as collaboration revenue. For the period

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

April 27, 2015 through December 31, 2015, the Company recognized the non-contingent consideration allocated to this unit of accounting of \$7.6 million as collaboration revenue.

- Committee participations under the 2010 Agreement and AG-881 Agreements: The Company developed the best estimate of selling price of the committee participation services of \$0.8 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, through the fourth quarter of 2016. During the period January 1, 2016 through May 17, 2016, the Company recognized the non-contingent consideration allocated to this unit of accounting \$89 thousand as collaboration revenue. For the period April 27, 2015 through December 31, 2015, the Company recognized the non-contingent consideration allocated to this unit of accounting of \$0.1 million as collaboration revenue.

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 estimates for on-going development services. The allocable consideration will increase as the Company performs certain services for which it is eligible to receive additional consideration. 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. The estimated arrangement consideration may decrease if the Company receives less reimbursement than initially estimated.

As a result of Celgene assuming the primary development responsibilities for enasidenib in the first quarter of 2015, the Company recorded \$0.9 million of third-party costs incurred on behalf of Celgene, during period January 1, 2016 through May 17, 2016, and \$3.0 million, for the period April 27, 2015 through December 31, 2015, as a reduction of research and development costs.

Beginning in the third quarter of 2015, the Company initiated a phase 1b frontline combination clinical trial of enasidenib and ivosidenib (AG-120) for which it will receive reimbursement. The new combination trial was determined to be a substantive option under the 2010 Agreement. When considering the factors included within ASC 605-45, management determined that the Company is the principal for the efforts related to the enasidenib arm of the combination trial but is acting in the role of an agent for the efforts related to the ivosidenib (AG-120) arm of the combination trial. Accordingly, consideration earned related to the enasidenib arm of the combination trial is recognized as collaboration revenue in the period earned and consideration earned related to the ivosidenib (AG-120) arm of the combination trial is reported as a reduction of research and development expense in the period earned. During the period January 1, 2016 through May 17, 2016, the Company recognized \$1.2 million in collaboration revenue and recorded \$0.3 million as a reduction of research and development costs related to the combination trial. For the year ended December 31, 2015, the Company recognized \$1.0 million in collaboration revenue and recorded \$0.1 million as a reduction of research and development costs related to the combination trial.

During the period January 1, 2016 through May 17, 2016, the Company incurred an additional \$4.4 million in reimbursable development expenses related to the ivosidenib (AG-120) and AG-881 programs that were not contemplated as of the April 2015 modification. The amounts are recorded as a reduction of research and development costs of each respective program.

*Post-May 2016*

The 2016 Agreement, executed on May 17, 2016, was determined to be a modification of the 2010 Agreement and the AG-881 Agreements because it includes compounds originally identified within the 2010 Agreement. As

Agios Pharmaceuticals, Inc.

Notes to Consolidated Financial Statements (continued)

a result of the modification the Company identified the undelivered elements under the Collaboration Agreements and determined the 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, the upfront payment of \$200.0 million under the 2016 Agreement and other consideration under the Collaboration Agreements that were deemed to be determinable at the modification date, to each unit of accounting relative to its best estimate of selling price. 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 at May 17, 2016, and the method of recognizing the allocated consideration, for each unit of accounting are as follows:

- Three separate development services for which the Company determined it is acting as the principal of all development activities (each of which is a separate unit of accounting): The Company developed the best estimate of selling price for all three of the development services of \$67.8 million using management's best estimate of the cost of obtaining these services at arm's length 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 services to be performed through 2019. When considering the factors included within ASC 605-45, the Company determined it is the principal of all development activities and is required to present reimbursement of amounts incurred for these services as revenue. For the period May 17, 2016 through December 31, 2016, the Company recognized the non-contingent consideration allocated to these units of accounting of \$21.3 million as collaboration revenue.
- Three separate on-going development services for which the Company determined it is not acting as the principal of all development activities (each of which is a separate unit of accounting): The Company developed the best estimate of selling price for all three development services of \$22.4 million using management's best estimate of the cost of obtaining these services at arm's length 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 on a proportional performance basis as services are provided. The Company expects the services to be performed through 2019. When considering the factors included within ASC 605-45, the Company determined it is not the principal of all development activities and is required to present reimbursement of amounts incurred for these services on a net basis as a reduction of research and development expenses. For the period May 17, 2016 through December 31, 2016, the Company recognized the non-contingent consideration allocated to these units of accounting of \$5.7 million as a reduction of research and development costs related to these services.
- On-going research and development: The Company developed the best estimate of selling price of the research and development services of \$207.0 million using management's best estimate of the cost of obtaining these services at arm's length from a third-party provider. The amount allocated to this unit of accounting is being recognized as revenue ratably through May 2022, the expected performance period. For the period May 17, 2016 through December 31, 2016, the Company recognized the non-contingent consideration allocated to this unit of accounting of \$14.4 million as collaboration revenue.
- Committee participations under the Collaboration Agreements: The Company developed the best estimate of selling price of the committee participation services of \$1.5 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 expected performance period, December 2022. For the period May 17, 2016 through December 31, 2016, the

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

Company recognized the non-contingent consideration allocated to this unit of accounting of \$92 thousand as collaboration revenue.

- Additional development activities for which the Company determined it is acting as the principal of all development activities: The Company developed the best estimate of selling price of the development service of \$48.7 million using management's best estimate of the cost of obtaining these services at arm's length 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 activities under this unit of accounting are not expected to begin until 2020. When considering the factors included within ASC 605-45, the Company determined it is the principal of all development activities and is required to present reimbursement of amounts incurred for these services as revenue. For the period May 17, 2016 through December 31, 2016, the Company has not recognized any revenue associated with this unit of accounting.

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 estimates for on-going development services. The allocable consideration will increase as the Company performs certain services for which it is eligible to receive additional consideration. 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. The estimated arrangement consideration may decrease if the Company receives less reimbursement than initially estimated.

During the three months ended December 31, 2016, the Company reached a preclinical achievement for a program that resulted in a change in estimate of total level of effort required for that program. This change in estimate resulted in the recognition of an additional \$10.8 million of revenue and reduced our net loss by the same amount for the year ended December 31, 2016. This also resulted in a decrease in net loss per share of \$0.28 over the same period.

As a result of Celgene assuming the primary development responsibilities for enasidenib in the first quarter of 2015, the Company recorded \$1.0 million of third-party costs incurred on behalf of Celgene for the period May 17, 2016 through December 31, 2016 as a reduction of research and development costs.

During the period May 17, 2016 through December 31, 2016, the Company incurred an additional \$0.2 million in reimbursable development expenses related to the enasidenib program that were not contemplated as of the May 2016 modification. The amount is recorded as collaboration revenue.

During the years ended December 31, 2016, 2015 and 2014, the Company recognized a total of \$44.9 million \$59.1 million and \$65.4 million, respectively, as collaboration revenue. The Company recognized \$19.7 million, \$25.2 million as a reduction of research and development expenses during the years ended December 31, 2016 and 2015, respectively. The Company did not recognize any reduction to research and development expenses in the year ended December 31, 2014.

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. As of December 31, 2016 and 2015, the Company has recorded a collaboration receivable of \$4.9 million and \$8.2 million, respectively, related to reimbursable development costs.

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

***Accounting analysis and revenue recognition – milestone revenue***

The Company concluded that certain of the clinical development and regulatory milestone payments that may be received under the Collaboration Agreements, 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. Revenue from substantive milestones, if they are nonrefundable, is 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.

In January 2016, a substantive clinical development milestone related to the enasidenib program under the 2010 Agreement was achieved and the Company received a milestone payment of \$25.0 million, which was recognized as collaboration revenue during the three months ended March 31, 2016. No other milestones were earned during the years ended December 31, 2016, 2015 and 2014. The next potential milestones expected to be achieved under the Collaboration Agreements relate to specified ex-U.S. regulatory events. Achievement of these events will result in milestone payments of up to \$70.0 million.

**4. Property and Equipment**

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

	<b>December 31,</b>	
	<b>2016</b>	<b>2015</b>
Laboratory equipment	\$ 14,529	\$ 9,751
Computer equipment and software	3,204	2,029
Leasehold improvements	19,858	15,853
Furniture and fixtures	748	413
Office equipment	233	206
Construction in progress	137	2,632
Total property and equipment	38,709	30,884
Less accumulated depreciation	(13,372)	(7,664)
Total property and equipment, net	<u>\$ 25,337</u>	<u>\$ 23,220</u>

Depreciation expense for the years ended December 31, 2016, 2015 and 2014 was \$5.7 million, \$3.3 million and \$1.4 million, respectively.

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

### 5. Accrued Expenses and Other Current Liabilities

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

	December 31,	
	2016	2015
Accrued compensation	\$ 11,092	\$ 7,005
Accrued contracted research and development costs	20,266	7,449
Accrued professional fees	476	228
Accrued other	168	1,314
<b>Total</b>	<b>\$ 32,002</b>	<b>\$ 15,996</b>

### 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 preexisting lease under which the Company leased 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 "First Amendment") to expand the rentable square footage of the leased space at 88 Sidney Street to approximately 113,200 square feet. The Company became responsible for paying rent under the Lease as amended by the First Amendment on May 15, 2015. The Company's lease at 38 Sidney Street terminated on June 15, 2015. On July 20, 2015, the Company entered into a second amendment to the Lease (the "Second Amendment") to expand the rentable square footage at 88 Sidney Street to approximately 146,030 square feet. The Company became responsible for paying for the additional space under the Second Amendment on November 1, 2015.

The initial term of the Lease, including both amendments, will terminate on May 15, 2022. At the end of the initial 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 Company gained physical access to the original space per the Lease in September 2014, the expanded space under the First Amendment in November 2014 and the expanded space under the Second Amendment in July 2015. Rent expense is recorded on a straight-line basis from the date physical access to the space was provided through the end of the lease term.

The Lease, including both amendments, contains rent escalation clauses and a tenant improvement allowance of \$20.5 million. The Company provided a standby letter of credit of \$2.9 million as security for its obligations under the Lease and both amendments in July 2015. The Company was not required to maintain any cash collateral for the standby letter of credit.

As of December 31, 2016 and 2015, the Company recorded approximately \$3.1 million and \$3.4 million, respectively, in tenant improvement allowance to be received from the Company's landlord. Amounts received for tenant improvements, which are considered normal tenant improvements are recorded as leasehold improvements within property and equipment, net, or construction in progress 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.

Agios Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

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

2017	\$ 9,050
2018	9,278
2019	9,511
2020	9,751
2021	9,996
Thereafter	3,903
	<u>\$ 51,489</u>

Rent expense was \$6.0 million, \$7.1 million and \$3.7 million for the years ended December 31, 2016, 2015 and 2014, respectively. The operating lease requires 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.

***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. During the years ended December 31, 2016 and 2015, the Company paid annual maintenance payments totaling \$70,000 and \$53,000, respectively, 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 \$70,000 for 2017. The Company could be required to make patent-related, clinical development, regulatory and sales-based milestone payments of up to \$0.1 million, \$1.6 million, \$5.4 million and \$3.7 million, respectively, to the licensors. As of December 31, 2016, the Company accrued \$75,000 and \$500,000 related to patent milestones and clinical milestones, respectively, that have been achieved. 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 \$70,000, \$135,000 and \$83,000 during the years ended December 31, 2016, 2015 and 2014, respectively. The Company incurred expenses of \$50,000 for a patent-related milestone in the year ended December 31, 2014 and incurred expenses of \$500,000 for a clinical milestone in the year ended December 31, 2016. The Company did not incur any milestones in 2015 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

Agios Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

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 Company has accrued a milestone payment of \$4.1 million for the accumulated discounted labor costs as of December 31, 2016.

***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.

**7. Common Stock**

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.

**8. Share-Based Payments**

***Stock incentive plans***

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 Company's initial public offering 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. Following the adoption of the 2013 Plan, the Company granted no further stock options or other awards under its 2007 Stock Incentive Plan (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, 2016, the total number of shares reserved under the 2007 Plan and the 2013 Plan are 6,256,099 and the Company had 759,556 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, 2017 and 2016, the annual increase for the 2013 Plan resulted in an additional 1,688,817 shares and 1,507,860 shares, respectively, authorized for issuance.

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

During the years ended December 31, 2016, 2015 and 2014 the Company did not grant any stock options to consultants and advisors of the Company.

The following table summarizes the stock option activity of all stock incentive plans for the year ended December 31, 2016.

	Number of Stock Options	Weighted- Average Exercise Price	Weighted- Average Remaining Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding at December 31, 2015	4,618,697	\$ 44.45	7.49	\$ 153,573
Granted	1,556,240	43.99		
Exercised	(603,359)	10.84		
Forfeited/Expired	(352,698)	65.21		
Outstanding at December 31, 2016	<u>5,218,880</u>	\$ 46.79	7.28	\$ 63,559
Exercisable at December 31, 2016	<u>2,527,605</u>	\$ 36.50	5.85	\$ 53,952
Vested and expected to vest at December 31, 2016	<u>5,065,064</u>	\$ 46.43	7.23	\$ 63,351

The weighted-average grant date fair value of options granted was \$28.41, \$65.38 and \$27.26 during the years ended December 31, 2016, 2015 and 2014, respectively. The total intrinsic value of options exercised was \$26.4 million \$50.9 million and \$60.4 million during the years ended December 31, 2016, 2015 and 2014, respectively.

At December 31, 2016, the total unrecognized compensation expense related to unvested stock option awards, including estimated forfeitures, was \$81.7 million, which the Company expects to recognize over a weighted-average period of approximately 2.5 years. The Company also has unrecognized stock-based compensation expense of \$11.6 million related to stock units with performance-based vesting criteria that are not considered probable of achievement as of December 31, 2016.

*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 Company granted 69,550 RSUs, 15,000 RSUs and 10,000 RSUs during the years ended December 31, 2016, 2015 and 2014, respectively. The Company recorded stock-based compensation expense related to RSUs of \$2.0 million, \$0.9 million and \$0.1 million for the years ended December 31, 2016, 2015 and 2014, respectively. These amounts are included in the total stock-based compensation expense disclosed within the table contained in the “Stock-based compensation expense” section of this footnote. As of December 31, 2016, there was approximately \$2.1 million of total unrecognized compensation expense related to RSUs, which is expected to be recognized over a weighted-average period of 1.1 years.

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

The following table presents RSU activity for the year ended December 31, 2016:

	<b>Number of Stock Units</b>	<b>Weighted-average grant date fair value</b>
Unvested shares at December 31, 2015	15,000	\$ 122.22
Granted	69,550	41.77
Vested	(7,500)	122.22
Unvested shares at December 31, 2016	<u>77,050</u>	<u>\$ 49.60</u>

*Performance-based stock options*

During the years ended December 31, 2016, 2015 and 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. However, certain performance-based stock options issued in prior periods were still outstanding as of December 31, 2016. Performance-based vesting criteria for options primarily relate to milestone events specific to the Company's corporate goals, including but not limited to certain preclinical, clinical and regulatory 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, 2016, certain of the performance-based milestones had been achieved. The achievements of all remaining milestones have been deemed probable as of December 31, 2016 and therefore the related expense either has been fully recognized or is being recognized over the remaining service period. During the years ended December 31, 2016, 2015 and 2014, the Company recognized stock-based compensation expense of \$0.9 million, \$0.4 million and \$0.9 million, respectively, related to stock options with performance-based vesting criteria.

*Performance-based stock units*

The Company may grant awards of performance stock units ("PSUs") to non-employee directors, members of the management team and employees on a discretionary basis pursuant to the 2013 Plan. Each PSU entitles the holder to receive, at the achievement of the performance-based and service-based criteria, a specified number of shares of the Company's stock. Performance-based vesting criteria primarily relate to milestone events specific to the Company's corporate goals, specifically regulatory development milestones related to the Company's product candidates.

The Company granted 114,503 PSUs and 100,270 PSUs during the years ended December 31, 2016 and 2015, respectively. Stock-based compensation expense associated with these PSUs is recognized if the performance condition is considered probable of achievement using management's best estimates. As of December 31, 2016, these milestones were not probable and, therefore, no expense has been recognized related to these awards. No such awards were granted during the year ended December 31, 2014.

The following table presents PSU activity for the year ended December 31, 2016:

	<b>Number of Stock Units</b>	<b>Weighted-average grant date fair value</b>
Unvested shares at December 31, 2015	100,270	\$ 64.44
Granted	114,503	45.02
Vested	—	—
Forfeited/expired	(14,160)	64.44
Unvested shares at December 31, 2016	<u>200,613</u>	<u>\$ 53.36</u>

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

*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 is 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 Company issued 36,680 shares and 17,150 shares during the years ended December 31, 2016 and 2015 under the 2013 ESPP. No shares were issued during the year ended December 31, 2014. The 2013 ESPP provides participating employees with the opportunity to purchase up to an aggregate of 327,272 shares of the Company's common stock. As of December 31, 2016, the Company had 273,442 shares available for future issuance under the 2013 ESPP.

The Company recorded \$0.8 million, \$0.4 million and \$0.1 million of stock-based compensation expense for the years ended December 31, 2016, 2015 and 2014, respectively, related to the 2013 ESPP.

*Stock-based compensation expense*

During the years ended December 31, 2016, 2015 and 2014, the Company recorded stock-based compensation expense for employee and non-employee stock options, restricted stock units, performance-based stock options, performance-based stock units and employee stock purchase plan shares. Expenses related to these equity-based awards were allocated as follows in the consolidated statements of operations (in thousands):

	<b>Years Ended December 31,</b>		
	<b>2016</b>	<b>2015</b>	<b>2014</b>
Research and development expense	\$ 25,386	\$ 17,419	\$ 6,688
General and administrative expense	16,700	14,544	4,818
	<u>\$ 42,086</u>	<u>\$ 31,963</u>	<u>\$ 11,506</u>

No related tax benefits were recognized for the years ended December 31, 2016, 2015 and 2014.

The fair value of each stock option granted to employees is estimated on the date of grant using the Black-Scholes option-pricing model. For non-employees, the fair value of each stock option is estimated on each vesting and reporting date 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:

	<b>Years Ending December 31,</b>		
	<b>2016</b>	<b>2015</b>	<b>2014</b>
Risk-free interest rate	1.42%	1.71%	1.83%
Expected dividend yield	—	—	—
Expected term (in years)	6.05	6.04	6.03
Expected volatility	72.84%	69.62%	78.61%

*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.

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

**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 alone does not have the relevant company-specific historical data to support its expected volatility. As such, the Company uses a weighted-average of expected volatility based on the volatilities of a representative group of publicly traded biopharmaceutical companies; this representative group also includes the Company. For purposes of identifying representative companies, the Company considered characteristics such as number of product candidates and their 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 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 uses historical data to estimate pre-vesting option forfeitures and records stock-based compensation expense only for those awards that are expected to vest. To the extent that actual forfeitures differ from the estimates, the difference is recorded as a cumulative adjustment in the period the estimates were revised. Stock-based compensation expense recognized in the financial statements is based on awards that are ultimately expected to vest.

**9. Income Taxes**

The domestic and foreign components of loss before income taxes are as follows, in thousands:

	<b>Years ended December 31,</b>		
	<b>2016</b>	<b>2015</b>	<b>2014</b>
Domestic	\$(179,896)	\$(111,057)	\$(53,930)
Foreign	(18,575)	(6,674)	—
Loss before income taxes	<u>\$(198,471)</u>	<u>\$(117,731)</u>	<u>\$(53,930)</u>

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

The provision (benefit) for income taxes is as follows for the years ended December 31, 2016, 2015 and 2014 (in thousands):

	Years Ended December 31,		
	2016	2015	2014
Current:			
Federal	\$ —	\$ —	\$ (444)
State	—	—	18
Foreign	—	—	—
Total current	—	—	(426)
Deferred:			
Federal	—	—	—
State	—	—	—
Foreign	—	—	—
Total deferred	—	—	—
Total	<u>\$ —</u>	<u>\$ —</u>	<u>\$ (426)</u>

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, 2016, 2015 and 2014:

	December 31,		
	2016	2015	2014
Income tax benefit computed at federal statutory tax rate	35.00%	35.00%	35.00%
State taxes, net of federal benefit	2.90	4.50	4.90
Change in valuation allowance	(43.40)	(44.60)	(35.80)
General business credits and other credits	9.50	8.40	(1.90)
Permanent differences	(0.20)	(0.20)	(0.10)
Incentive Stock Options	(1.80)	(1.80)	(2.00)
Foreign Rate Differential	(1.90)	(1.20)	—
Other	(0.10)	(0.10)	0.80
Total	<u>0.00%</u>	<u>0.00%</u>	<u>0.90%</u>

Agios Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

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, 2016 and 2015 are as follows (in thousands):

	<b>December 31,</b>	
	<b>2016</b>	<b>2015</b>
<b>Deferred tax assets:</b>		
Net operating loss carryforwards	\$ 126,077	\$ 81,947
Deferred revenue	8,051	7,046
Tax credit carryforwards	43,350	16,708
Purchased intangible assets	4,410	724
Stock-based compensation	22,731	11,923
Deferred rent	8,516	7,975
Non-deductible accruals and reserves	3,310	2,520
<b>Total deferred tax assets</b>	<b>216,445</b>	<b>128,843</b>
Valuation allowance	(208,033)	(121,874)
<b>Total deferred tax assets</b>	<b>\$ 8,412</b>	<b>\$ 6,969</b>
<b>Deferred tax liabilities:</b>		
Depreciation and amortization	\$ (8,412)	\$ (6,969)
<b>Total deferred tax liabilities</b>	<b>\$ (8,412)</b>	<b>\$ (6,969)</b>
<b>Net deferred tax asset</b>	<b>\$ —</b>	<b>\$ —</b>

As of December 31, 2016, the Company had net operating loss carryforwards available (NOLs) to reduce federal, state and foreign income taxes of approximately \$387.2 million, \$391.5 million and \$20.2 million, respectively. If not utilized, these carryforwards expire at various dates through 2036. At December 31, 2016, the Company also has available research and development tax credits for federal and state income tax purposes of approximately \$7.3 million and \$4.2 million, respectively. The Company engaged in clinical testing activities and incurred expenses that qualify for the federal orphan drug tax credit. At December 31, 2016, the Company has available orphan drug tax credits for federal purposes only of approximately \$33.3 million. If not utilized, the credits expire at various dates through 2036.

Included in the carryforwards above, the Company has federal and state NOLs related to stock compensation in the amount of \$81.9 million and \$77.8 million, respectively, which is not included in deferred tax assets. When the excess stock-based compensation related to the NOL carryover tax assets are realized, the benefit will be credited directly to stockholders' equity under the Company's current accounting policy. However, the Company will adopt ASU 2016-09, *Improvements to Employee Share-Based Payment Accounting*, during the quarter ended March 31, 2017. As a result of the adoption, the net operating losses deferred tax assets will increase by \$32.7 million and will be offset by a corresponding increase in the valuation allowance. The adoption of ASU 2016-09 will have no impact to the Company's income statement, balance sheet or retained earnings.

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.

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

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 five percent stockholders 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 Section 382 study through December 31, 2011, to determine whether any ownership change has occurred since the Company's formation and determined that transactions have resulted in two ownership changes, as defined by Section 382. 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 after December 31, 2011 that could further limit the amount of NOLs and tax credit carryforwards that the Company can utilize. The Company will complete a full analysis of the tax attribute carryforwards prior to any utilization.

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. Based on the weight of available evidence, both positive and negative, management has recorded a valuation allowance of \$208.0 million and \$121.9 million at December 31, 2016 and December 31, 2015, respectively, because management has determined that it is more likely than not that these assets will not be fully realized. The valuation allowance increased by \$86.1 million in the year ended December 31, 2016.

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, 2016 and 2015, the Company had no unrecognized tax benefits. The Company recognizes interest and penalties related to uncertain tax positions in income tax expense.

The Company is subject to taxation in the United States and Switzerland. The statute of limitations for assessment by the Internal Revenue Service (IRS) and state tax authorities is open for tax years ending December 31, 2016, 2015, 2014, and 2013 although carryforward attributes that were generated for tax years prior to 2013 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. The statute of limitations for assessment in Switzerland remains open for tax year ending December 31, 2016 and 2015. There are currently no federal, state or foreign audits in progress.

#### **10. 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 will make matching contributions equal to 50% of the employee's contributions, subject to a maximum of 6% of eligible compensation. During the year ended December 31, 2016 and 2015, the Company provided \$1.0 million and \$0.7 million, respectively, in contributions to this plan. The Company did not provide any contributions during the year ended December 31, 2014.

Agius Pharmaceuticals, Inc.  
Notes to Consolidated Financial Statements (continued)

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

<b>2016</b>	<b>First Quarter</b>	<b>Second Quarter</b>	<b>Third Quarter</b>	<b>Fourth Quarter</b>
	<b>(In thousands, except per share data)</b>			
Total revenue	\$ 31,281	\$ 6,978	\$ 8,985	\$ 22,648
Loss from operations	(23,594)	(56,470)	(63,512)	(57,409)
Net loss	(23,198)	(55,953)	(62,834)	(56,486)
Net loss per share – basic and diluted	(0.61)	(1.47)	(1.63)	(1.34)
<b>2015</b>	<b>First Quarter</b>	<b>Second Quarter</b>	<b>Third Quarter</b>	<b>Fourth Quarter</b>
	<b>(In thousands, except per share data)</b>			
Total revenue	\$ 34,202	\$ 13,219	\$ 5,480	\$ 6,218
Loss from operations	(5,195)	(32,133)	(40,475)	(40,897)
Net loss	(4,957)	(31,897)	(40,257)	(40,621)
Net loss per share – basic and diluted	(0.13)	(0.85)	(1.07)	(1.08)

**EXHIBIT INDEX**

<b>Exhibit Number</b>	<b>Description of Exhibit</b>	<b>Incorporated by Reference</b>			<b>Exhibit Number</b>	<b>Filed Herewith</b>
		<b>Form</b>	<b>File Number</b>	<b>Date of Filing</b>		
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	

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[Table of Contents](#)

<b>Exhibit Number</b>	<b>Description of Exhibit</b>	<b>Incorporated by Reference</b>			<b>Exhibit Number</b>	<b>Filed Herewith</b>
		<b>Form</b>	<b>File Number</b>	<b>Date of Filing</b>		
10.10#	Letter Agreement, dated as of July 22, 2010, between the Registrant and Scott Biller, Ph.D.	S-1	333-189216	July 11, 2013	10.10	
10.11#	Letter of Agreement, dated May 4, 2010 between the Registrant and Glenn Goddard	S-1	333-189216	June 10, 2013	10.11	
10.12	Form of Indemnification Agreement between the Registrant and each of its Executive Officers and Directors	S-1	333-189216	July 11, 2013	10.12	
10.13#	Letter Agreement, dated as of April 1, 2014, between the Registrant and Christopher Bowden, Ph.D.	10-K	001-36014	February 26, 2016	10.13	
10.14	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	
10.15†	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	
10.16†	Third Amendment to Discovery and Development Collaboration and License Agreement, dated July 14, 2014 between the Registrant and Celgene Corporation	10-K	001-36014	February 24, 2015	10.15	
10.17	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	

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[Table of Contents](#)

<u>Exhibit Number</u>	<u>Description of Exhibit</u>	<u>Incorporated by Reference</u>			<u>Exhibit Number</u>	<u>Filed Herewith</u>
		<u>Form</u>	<u>File Number</u>	<u>Date of Filing</u>		
10.18	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	
10.19	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	
10.20	First Amendment to Lease, dated as of November 21, 2014, between the Registrant and Forest City 88 Sidney, LLC	8-K	001-36014	November 26, 2014	10.1	
10.21#	Summary Description of Annual Cash Incentive Program	10-Q	001-36014	May 11, 2015	10.1	
10.22	Second Amendment to Lease for 88 Sidney Street, dated July 20, 2015, by and between Agios Pharmaceuticals, Inc. and Forest City 88 Sidney Street, LLC	8-K	001-36014	July 23, 2015	10.1	
10.23†	Collaboration and License Agreement by and between Agios Pharmaceuticals, Inc. and Celgene Corporation Re: AGI-23088 for the US Territory, dated as of April 27, 2015	10-Q	001-36014	August 7, 2015	10.1	
10.24†	Collaboration and License Agreement by and between Agios International Sarl and Celgene International II Sarl Re: AGI-23088 for the ROW Territory, dated as of April 27, 2015	10-Q	001-36014	August 7, 2015	10.2	
10.25#	Form of Performance Share Unit Agreement under 2013 Stock Incentive Plan	10-K	001-36014	February 26, 2016	10.25	

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[Table of Contents](#)

<b>Exhibit Number</b>	<b>Description of Exhibit</b>	<b>Incorporated by Reference</b>			<b>Exhibit Number</b>	<b>Filed Herewith</b>
		<b>Form</b>	<b>File Number</b>	<b>Date of Filing</b>		
10.26#	Severance Benefits Plan	8-K	001-36014	April 22, 2016	10.21	
10.27#	Letter Agreement, dated as of January 7, 2016, between the Registrant and Steve Hoerter	10-Q	001-36014	May 9, 2016	10.1	
10.28†	Master Research and Collaboration Agreement, dated May 17, 2016, by and among the Registrant, Celgene Corporation and Celgene RIVOT Ltd.	10-Q	001-36014	August 8, 2016	10.1	
10.29#	Letter Agreement between Agios Pharmaceuticals, Inc. and Andrew Hirsch, effective August 11, 2016	8-K	001-36014	August 16, 2016	99.2	
21.1	Subsidiaries of the Registrant					X
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

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[Table of Contents](#)

<u>Exhibit Number</u>	<u>Description of Exhibit</u>	<u>Incorporated by Reference</u>			<u>Exhibit Number</u>	<u>Filed Herewith</u>
		<u>Form</u>	<u>File Number</u>	<u>Date of Filing</u>		
101.INS	XBRL Instance Document					X
101.SCH	XBRL Taxonomy Extension Schema Document					X
101.CAL	XBRL Taxonomy Calculation Linkbase Document					X
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.

\* This certification will not be deemed “filed” for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the “Exchange Act”), or otherwise subject to the liability of that section. Such certification will not be deemed to be incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act, except to the extent specifically incorporated by reference into such filing. This certification will not be deemed “filed” for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the “Exchange Act”), or otherwise subject to the liability of that section. Such certification will not be deemed to be incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act, except to the extent specifically incorporated by reference into such filing.

Subsidiaries

Entity

Agios Securities Corporation  
Agios International Sarl

State or other Jurisdiction of Incorporation or  
Organization

Massachusetts  
Switzerland

**CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM**

We consent to the incorporation by reference in the Registration Statements (Form S-8 Nos. 333-209755, 333-201796, 333-193802 and 333-190101 and Form S-3 No. 333-200822) of Agios Pharmaceuticals, Inc. of our reports dated February 16, 2017 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, 2016.

/s/ Ernst & Young LLP

Boston, Massachusetts  
February 16, 2017

## 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 16, 2017

/s/ David P. Schenkein

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

## CERTIFICATION

I, Andrew Hirsch, 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 16, 2017

/s/ Andrew Hirsch

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Andrew Hirsch  
Chief Financial Officer  
(principal financial officer)

**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, 2016, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, David P. Schenkein, President and 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 16, 2017

/s/ David P. Schenkein

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

**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, 2016, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Andrew Hirsch, Chief Financial 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 16, 2017

/s/ Andrew Hirsch

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Andrew Hirsch  
Chief Financial Officer  
(principal financial officer)

