AGIOS PHARMACEUTICALS INC
Form 10-K
February 14, 2018
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UNITED STATES SECURITIES AND EXCHANGE COMMISSION
Washington, DC 20549
Form 10-K
(Mark One)
ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2017
OR
TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
Commission File Number:
001-36014
AGIOS PHARMACEUTICALS, INC.
(Exact name of registrant as specified in its charter)

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

Registrant's telephone number, including area code:
(617) 649-8600
Securities registered pursuant to Section 12(b) of the Act:

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

Securities registered pursuant to Section 12(g) of the Act: None
Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes No
Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes No
Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes No
Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to

submit and post such files). Yes No

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

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

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

If an emerging growth company, indicate by check mark if the registrant has elected not to use the transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

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, 2017 (based on the last reported sale price on the NASDAQ Global Select Market as of such date) was $2,154,093,268.

As of February 9, 2018, there were 57,326,741 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 2018 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, 2017 are incorporated by reference into Part III of this Annual Report on Form 10-K to the extent stated herein.

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PART I

References to Agios

Throughout this Annual Report on Form 10-K, "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," "c 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 isocitrate dehydrogenase 2 and 1, or IDH2 and IDH1, respectively, and pyruvate kinase-R mutations, methionine adenosyltransferase 2a, or MAT2A, and dihydroorotate dehydrogenase, or DHODH, as therapeutic targets;
- the potential benefits of our product candidates targeting IDH2, IDH1 or pyruvate kinase-R mutations, MAT2A or DHODH, including IDHIFA®, ivosidenib, AG-881, AG-348, and AG-270;
- our plans to develop and commercialize our product candidates, including our ability to successfully commercialize IDHIFA® with our partner Celgene Corporation, or Celgene, and to obtain regulatory approval for, and successfully commercialize, ivosidenib;
- our collaborations with Celgene and related subsidiaries;
- our ability to establish and maintain additional collaborations or obtain additional funding;
- the timing or likelihood of regulatory filings and approvals, including our new drug application, or NDA, filed in December 2017 with the U.S. Food and Drug Administration, or FDA, for ivosidenib for the treatment of adult patients with relapsed or refractory acute myeloid leukemia, or R/R AML with an IDH1 mutation, and the Marketing Authorization, or MAA, we plan to submit to the European Medicines Agency, or EMA, in the fourth quarter of 2018 for ivosidenib for IDH1 mutant-positive R/R AML;
- the implementation of our business model and 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.

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

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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 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 diseases, or RGDs, which are diseases that are directly caused by changes in genes or chromosomes, often passed from one generation to the next. Most RGDs are often associated with severe or life-threatening features. The incidence of a single RGD can vary widely but is generally very infrequent, usually equal to or less than one per 100,000 births. In both areas of cancer and RGDs, we are seeking to unlock the biology of cellular metabolism as a platform to create transformative therapies.

Our first commercial cancer product is IDHIFA®. In August 2017, the FDA granted our collaboration partner Celgene Corporation, or Celgene, approval of IDHIFA® for the treatment of adult patients with R/R AML, and an IDH2 mutation as detected by an FDA-approved test. IDHIFA®, an oral targeted inhibitor of the mutated IDH2 enzyme, is the first and only FDA-approved therapy for patients with R/R AML and an IDH2 mutation.

Our most advanced clinical cancer product candidates are ivosidenib, which targets mutated IDH1, and AG-881, which is a brain-penetrant pan-IDH mutant inhibitor. These mutations are found in a wide range of hematological malignancies and solid tumors. In December 2017, we submitted a new drug application, or NDA, to the FDA for ivosidenib for the treatment of patients with R/R AML and an IDH1 mutation. We plan to submit an MAA to the EMA for ivosidenib for IDH1 mutant-positive R/R AML in the fourth quarter of 2018.

Our next most advanced cancer product candidate is AG-270, an inhibitor of MAT2A. We submitted an investigational new drug application, or IND, for AG-270 in November 2017, and in December 2017 the FDA concluded that we may proceed with our planned phase 1 dose-escalation trial of AG-270 in multiple tumor types carrying a methylthioadenosine phosphorylase, or MTAP, deletion. We expect to initiate this trial in the first quarter of 2018.

Our most advanced preclinical cancer product candidate is an inhibitor of the metabolic enzyme DHODH. We plan to submit an IND for our DHODH inhibitor for the treatment of hematologic malignancies in the fourth quarter of 2018.

The lead product candidate in our RGD program, AG-348, targets pyruvate kinase-R for the treatment of pyruvate kinase, or PK, deficiency. PK deficiency is a rare genetic disorder that often results in severe hemolytic anemia, jaundice and lifelong conditions associated with chronic anemia and secondary complications due to inherited mutations in the pyruvate kinase enzyme within red blood cells, or RBCs. We intend to initiate two global, pivotal trials of AG-348 in PK deficiency in the first half of 2018: ACTIVATE-T, a single arm trial of approximately 20 regularly transfused patients, is expected to initiate in the first quarter of 2018, and ACTIVATE, a 1:1 randomized, placebo-controlled trial of approximately 80 patients who do not receive regular transfusions, is expected to initiate in the second quarter of 2018. We also expect to initiate a phase 2 proof of concept trial of AG-348 in thalassemia in the fourth quarter of 2018.

In addition to the aforementioned development programs, we are seeking to advance a number of early-stage discovery programs in the areas of cancer metabolism, RGDs and metabolic immuno-oncology, or 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.

The clinical development strategy for all of our product and development 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 would 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.

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- Maintaining our competitive advantage and focus in the field of cellular metabolism by building a research platform in cancer metabolism, RGDs and MIO.
- Collaborating closely with the FDA and other regulatory bodies to aggressively pursue early registration potential for our product candidates, for example by utilizing a similar regulatory path for ivosidenib as Celgene did for IDHIFA®.
- Continuing to build a product engine for cancer and RGDs to generate novel and important medicines.
- Building a preeminent independent biopharmaceutical company by engaging in discovery, development and commercialization of our medicines.
- Maintaining a commitment to precision medicine in drug development.

Our Guiding Principles

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

- Follow the science and do what is right for patients.
- Maintain a culture of incisive decision-making driven by deep scientific interrogation and “respectful irreverence.”
- Foster 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 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.

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Cytotoxic chemotherapies

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

Targeted therapies

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

Emerging areas

Several new approaches to develop novel cancer treatments are underway. They include: treatment with drugs or other methods that stimulate the normal immune system to attack the cancer (immuno-oncology), including immunotherapies based on chimeric antigen receptor and T cell receptor technologies to genetically engineer T cells to recognize and kill cancer cells; antibody drug conjugates (e.g., Kadcyla®) that carry a powerful chemotherapy payload that is only released into the cancer cell; and drugs that target the changes in gene activity that occurs in cancer cells (epigenetics).

Cancer metabolism is an 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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Rare genetic diseases

RGDs, a subset of orphan genetic metabolic diseases, are a broad group of more than 600 rare 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, or E.U. In a study in British Columbia, the overall incidence of RGDs was estimated to be 70 per 100,000 live births or one in 1,400 births, overall representing more than approximately 15% of single gene disorders in the population. Incidence of a single RGD can vary widely but is generally rare, usually equal to or less than one per 100,000 births. Many RGDs are likely to be under-diagnosed given the lack of available therapies or diagnostics and the rarity of the condition.

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

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

We focus on RGDs that share the following common set of features:

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

Precision Medicine Approach

Our understanding of cellular metabolism within diseased tissues enables the development of methods to measure the effect of a drug on the target of interest and the patient, or pharmacodynamic markers, and patient selection strategies for clinical development 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.

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.

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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 summarizes our most advanced product candidates as of February 1, 2018, each of which is described in further detail below:

Targeting Mutated IDH for the Treatment of Cancer

The 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 (a-ketoglutarate), both of which are critically important for cellular function and the creation of energy. In

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humans, there are three forms of the IDH enzyme, IDH1, IDH2, and IDH3, but only IDH1 and IDH2 appear to be mutated in cancers. IDH1 and IDH2 catalyze the same reaction but in different cellular compartments: IDH1 is found in the cytoplasm of the cell and IDH2 in the mitochondria. Tumor cells are generally observed to carry either an IDH1 or IDH2 mutation.

Using our proprietary metabolic platform, we and our collaborators examined the mutated pathway and discovered that the mutated IDH enzymes had adopted a novel "gain of function" activity that allows only the mutated IDH enzyme to produce large amounts of a metabolite called 2-hydroxygluturate, or 2HG. We 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 IDHIFA® and ivosidenib, our lead inhibitors of mutant IDH2 and IDH1, respectively, demonstrate evidence of cellular differentiation, normalization of cell counts and mutational clearance in the bone marrow and blood, a mechanism of response that is consistent with preclinical studies, including substantial reduction of plasma 2HG levels. This targeted differentiation effect is distinct from that seen with traditional cytotoxic chemotherapeutics, which lead to cell death, commonly used to treat cancer. Our goal is to establish our IDH mutation inhibitors as a cornerstone of AML therapy spanning all treatment lines.

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 estimates on the occurrence of IDH2 and IDH1 mutations in certain hematologic and solid tumors. We believe our estimates may expand as more cancer treatment centers screen for these IDH mutations.

Mutation	Indications	% with IDH mutations
IDH1	AML	~6-10%
	Cholangiocarcinoma	~14%
	Low grade glioma	~80%
IDH2	AML	~9-13%

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

IDHIFA®

IDHIFA® 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 August 2017, the FDA granted Celgene approval of IDHIFA® for the treatment of adult patients with R/R AML and an IDH2 mutation as detected by an FDA-approved test.

Celgene maintains worldwide development and commercial rights to IDHIFA® and will fund the future development and commercialization costs related to this program. Under the 2010 Agreement described below, Celgene is responsible for all development costs for IDHIFA®, and we are eligible to receive up to $95.0 million in milestone payments, which are comprised of: (i) up to $70.0 million in milestone payments upon achievement of specified ex-U.S. regulatory milestone events and (ii) a $25.0 million milestone payment upon achievement of a specified commercial milestone event. Additionally, we are eligible to receive royalties at tiered low-double digit to mid-teen percentage rates on any net sales of IDHIFA®. 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 IDHIFA® development program under the 2010 Agreement. We also have co-commercialization rights to provide up to one-third of the field-based commercialization efforts and will be reimbursed for those efforts.

We continue to evaluate IDHIFA® in clinical trials in patients with hematological cancers with IDH2 mutations, which are led and funded by Celgene. To date, all clinical data reported by us and our collaborators in hematological cancers highlight that the mechanism of response is consistent with preclinical studies, including substantial reduction

of plasma 2HG levels, as well as evidence of cellular differentiation and normalization of cell counts in the bone marrow and blood. This differentiation effect is distinct from that seen with traditional chemotherapeutics commonly used to treat AML. The FDA has granted orphan drug designation for IDHIFA® for treatment of patients with AML and fast track designation for treatment of patients with AML that harbor an IDH2 mutation, and the EMA granted orphan drug designation for IDHIFA® for the treatment of AML.

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We and Celgene are evaluating IDHIFA® in the following clinical trials:

Phase 1/2 clinical trial

The FDA's approval of IDHIFA® in R/R AML was based on clinical data from an open-label, single-arm, multicenter, two-cohort phase 1/2 clinical trial of adult patients with R/R AML and an IDH2 mutation. The safety of IDHIFA® was evaluated in 214 patients in this trial. The median duration of exposure to IDHIFA® was 4.3 months (range 0.3 to 23.6). The 30 and 60-day mortality rates observed with IDHIFA® were 4.2% (9 of 214 patients) and 11.7% (25 of 214 patients), respectively. In the clinical trial, 14% of patients treated with IDHIFA® experienced differentiation syndrome, which can be fatal if not treated. The most common adverse events, or AEs, seen in greater 20% of patients were nausea, vomiting, diarrhea, elevated bilirubin and decreased appetite. Serious adverse events, or SAEs, were reported in 77.1% of patients. The most frequent serious adverse reactions (greater than 2% of patients) were leukocytosis, diarrhea, nausea, vomiting, decreased appetite, tumor lysis syndrome, and differentiation syndrome. More than half (52%) of the treated patients were refractory to previous therapy. The efficacy of IDHIFA® was evaluated in 199 adult patients in the clinical trial. IDHIFA® was given orally at a starting dose of 100 mg daily until disease progression or unacceptable toxicity. Dose reductions were allowed to manage side effects. Patients had a median age of 68 years (range of 19 to 100) and received a median of two prior anticancer regimens (ranging from one to six). IDHIFA® demonstrated a combined CR or complete response with partial hematologic improvement, or CRh, rate of 23% (n=46) (95% CI: 18%, 30%). Median duration of CR/CRh was 8.2 months (95% CI: range 4.3, 19.4). For patients who achieved a CR/CRh, the median time to first response was 1.9 months (range, 0.5 to 7.5 months) and the median time to best response of CR/CRh was 3.7 months (range, 0.6 to 11.2 months). Of patients achieving a CR/CRh, 85% (39 of 46 patients) did so within six months of initiating IDHIFA®. 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. CRh is defined as less than 5% of blasts in the bone marrow, no evidence of disease and partial recovery of peripheral blood counts (platelets >50,000/lL and ANC >500/lL). Among the 157 patients who were dependent on RBCs and/or platelet transfusions at baseline, 53 (34%) became independent of RBCs and platelet transfusions during any 56-day post-baseline period. Of the 42 patients who were independent of both RBCs and platelet transfusions at baseline, 32 (76%) remained transfusion independent during any 56-day post-baseline period.

Phase 1b frontline combination trial

IDHIFA® is being evaluated in a phase 1b, multicenter, international, open-label clinical trial, conducted by us, to evaluate the safety and clinical activity of IDHIFA® or ivosidenib 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 IDHIFA® administered at an initial oral dose of 100 mg once daily in patients with an IDH2 mutation or ivosidenib administered at an initial oral dose of 500 mg once daily in patients with an IDH1 mutation. IDHIFA® or ivosidenib is 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.

In December 2017, we presented interim data from this trial at ASH 2017. As of the August 1, 2017 data cut-off, in the IDHIFA® arm, the most common grade 3 or higher non-hematologic AEs during the induction period were febrile neutropenia (63%), blood bilirubin increase (9%), hypertension (9%) and bacteremia (9%). The 30- and 60-day mortality rates were 5% and 7%, respectively. There was one dose-limiting toxicity in the IDHIFA® arm consisting of persistent Grade 4 thrombocytopenia lasting beyond 42 days from the start of induction. The median time to absolute neutrophil count, or ANC, recovery (greater than 500/μL) was 34 days (95% CI 29,35). The median time to platelet recovery (greater than 50,000/μL) was 33 days (95% CI 29,50). In the IDHIFA® arm the overall best response rate of combined CR and CRi/CRp, was 62% (31 of 50 response-evaluable patients); among 27 response-evaluable patients with de novo AML, the overall best response rate of combined CR and CRi/CRp was 67% (18 of 27 patients); and among 23 response-evaluable patients with secondary AML, the overall best response rate of combined CR and CRi/CRp was 57% (13 of 23 patients). A CRp, or complete remission with incomplete platelet recovery, means all the criteria for CR are met except that platelet counts are outside of the normal range. Platelets are one of the three major types of blood cells. A CRi, or complete remission with incomplete neutrophil or platelet recovery, 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. The interim reported results from the ivosidenib arm of this trial are discussed below under “Ivosidenib - Phase 1(b) frontline combination trial.”

Phase 1/2 frontline combination trial

IDHIFA® is being evaluated in a phase 1/2 frontline combination clinical trial, conducted by Celgene, of either IDHIFA® or ivosidenib 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 the IDHIFA® investigational combination versus single-agent VIDAZA® using a primary endpoint of overall response rate, or ORR. In the phase 1 component of the trial, patients received

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100 mg (n=3) or 200 mg (n=3) of IDHIFA® daily plus VIDAZA® or 500 mg of ivosidenib (n=11) plus VIDAZA®. The trial has completed the phase 1 component and is currently enrolling in the phase 2 component.

In December 2017, we presented interim data from this trial at ASH 2017. As of the September 1, 2017 data cut-off, the median age of patients treated in the IDHIFA® arm was 68 (five out of six patients were 65 years old or older), and the most common grade 3-4 hematologic AE was neutropenia (33%), with thrombocytopenia, febrile neutropenia, anemia, lymphocyte count decreased and white blood cell count decreased all with one event (17% each), and the most common grade 3-4 non-hematologic AEs were pneumonia (33%) and hyperbilirubinemia (33%). IDH differentiation syndrome was reported in one patient. In the IDHIFA® arm, four of six patients had a response, including two CRs, one partial remission, or PR, and one morphologic leukemia-free state, or MLFS. 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. The interim reported results from the ivosidenib arm of this trial are discussed below under “Ivosidenib - Phase 1/2 frontline combination trial.”

IDHENTIFY

IDHIFA® is being evaluated in IDHENTIFY, an international phase 3, multi-center, open-label, randomized clinical trial, conducted by Celgene, designed to compare the efficacy and safety of IDHIFA® 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 3 frontline combination trial

We plan to support, with Celgene, the initiation of an intergroup sponsored, global, registration-enabling phase 3 trial combining ivosidenib or IDHIFA® and standard induction (7+3) and consolidation chemotherapy with a primary endpoint of event-free survival in frontline AML patients with an IDH1 or IDH2 mutation in the fourth quarter of 2018. The trial is expected to enroll approximately 500 patients with an IDH1 mutation and approximately 500 patients with an IDH2 mutation.

Ivosidenib

Ivosidenib is our wholly owned, 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. The FDA has granted us fast track designation to ivosidenib for treatment of patients with AML that harbor an IDH1 mutation and orphan drug designation for ivosidenib for treatment of patients with AML. The FDA has also granted fast-track designation to ivosidenib for treatment of patients with previously treated, unresectable or metastatic cholangiocarcinoma with and IDH1 mutation. In December 2017, we submitted an NDA to the FDA for ivosidenib for the treatment of patients with R/R AML and an IDH1 mutation. We plan to submit an MAA to the EMA for ivosidenib for IDH1 mutant-positive R/R AML in the fourth quarter of 2018.

We are evaluating ivosidenib in the following clinical trials:

Phase 1 clinical trial (advanced hematologic malignancies)

Ivosidenib 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 is evaluating 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 is evaluating 25 untreated AML patients. The third cohort is evaluating 25 patients with other non-AML IDH1 mutant-positive relapsed or refractory advanced hematologic malignancies. The fourth cohort is evaluating patients with relapsed IDH1 mutant-positive AML not eligible for the first arm or standard of care chemotherapy. Ivosidenib is administered at a 500 mg once daily oral dose, in 28-day cycles. Enrollment to the trial is closed.

In December 2017, we presented interim clinical data from 258 patients treated with ivosidenib in the dose escalation and expansion arms of the trial at ASH 2017. Doses were administered from 200 mg to 1,200 mg total daily doses in

dose escalation and 500 mg daily in dose expansion. A maximum tolerated dose, or MTD, was not reached in the dose escalation portion of the trial. As of the May 12, 2017 data cut-off, a safety analysis conducted for all 258 treated patients showed that ivosidenib continues to demonstrate a favorable safety profile. The most common AEs regardless of causality were diarrhea (33.3%), leukocytosis (30.2%), nausea (29.5%), fatigue (28.7%) and febrile neutropenia (25.2%). The data included 125 R/R AML patients who were enrolled at least six months prior to the data-cutoff, comprised of 92 patients from arm 1 of the expansion and 33 patients from the dose-escalation who met the eligibility criteria for arm 1 and received ivosidenib at 500 mg once daily. Among these 125 R/R AML patients, 8% reported grade ³3 leukocytosis, which was managed with hydroxyurea (no

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cases were fatal), 8% reported grade 3 QT prolongation (ivosidenib was reduced in one patient, and no cases were grade 4 or fatal), and 9.6% reported IDH differentiation syndrome, which was managed with corticosteroids and diuretics (no cases were grade 4 or fatal). Data from 125 R/R AML patients demonstrated a combined CR and CRh rate of 30.4% (95% CI 22.5, 39.3), which is the primary endpoint of the study. The CR rate was 21.6% (27 of 125 patients) (95% CI 14.7, 29.8) and the CRh rate was 8.8% (11 of 125 patients). The ORR among the R/R AML patients was 41.6% (52 of 125 patients), and median duration of response was 9.3 months (95% CI 5.6, 18.3) for patients who achieved a CR, 8.2 months (95% CI 5.5, 12.0) for patients who achieved a CR/CRh and 6.5 months (95% CI 4.6, 9.3) for all patients who responded. The median time to first response was 1.9 months (0.8-4.7) for all patients who responded, median time to CR was 2.8 months (0.9-8.3) for patients who achieved a CR, and median time to CR/CRh was 2.7 months (0.9-5.6) for patients who achieved a CR/CRh. At the time of the data cut-off, median OS as observed in the study had not yet been reached for patients who achieved a CR/CRh. OS was 9.3 months (95% CI 3.7, 10.8) for non-CR/CRh responders, 3.9 months (95% CI 2.8, 5.8) for non-responders, and 8.8 months (95% CI 6.7, 10.2) overall. Of the patients who were transfusion dependent at baseline and achieved a CR, 100% became independent of platelet transfusions and 84.6% became independent of RBC transfusions during any 56-day post baseline period. Of the patients who were transfusion dependent at baseline and achieved a CRh, 71.4% became independent of platelet transfusions and 75.0% became independent of RBC transfusions during any 56-day post baseline period. Transfusion independence was also seen among non-CR/CRh responders and non-responders. Of the patients who were transfusion dependent at baseline and were non-CR/CRh responders, 58.3% became independent of platelet transfusions and 50% became independent of RBC transfusions during any 56-day post-baseline period. Of those who were transfusion dependent at baseline and were non-responders, 16.7% became independent of platelet transfusions and 15.4% became independent of RBC transfusions during any 56-day post-baseline period. Non-CR/CRh responders include patients with CRi, CRp and MLFS who are not CRh. An efficacy analysis was also presented for 34 untreated AML patients not eligible for standard of care therapies whose starting dose was 500 mg daily and 12 myelodysplastic syndrome, or MDS, patients in expansion cohorts whose starting dose was 500 mg daily. Data from 34 untreated AML patients demonstrated a 55.9% ORR and a CR rate of 20.6%. The median duration of response was 9.2 months (95% CI 1.9, NE), and median duration of CR has not yet been reached. Data from 12 MDS patients demonstrated a 91.7% ORR and a CR rate of 41.7%.

Phase 1b frontline combination trial

As discussed above, ivosidenib is being evaluated in a phase 1b, multicenter, international, open-label clinical trial to evaluate the safety and clinical activity of IDHIFA® or ivosidenib 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.

In December 2017, we presented interim data from this trial at ASH 2017. As of the August 1, 2017 data cut-off, in the ivosidenib arm, the most common grade 3 or higher non-hematologic AEs during the induction period were febrile neutropenia (60%), blood bilirubin increase (9%), hypertension (9%), colitis (9%), increased alanine aminotransferase (9%) and increased aspartate aminotransferase (9%). The 30- and 60-day mortality rates were both 6%, and there were no dose-limiting toxicities. The median time to ANC recovery (greater than 500/μL) was 28.5 days (95% CI 27,34). The median time to platelet recovery (greater than 50,000/μL) was 28 days (95% CI 26,34). In the ivosidenib arm, the overall best response rate of combined CR and CRi/CRp was 77% (23 of 30 response-evaluable patients); among 21 patients with de novo AML, the overall best response rate of combined CR and CRi/CRp was 91% (19 of 21 patients); and among nine patients with secondary AML, the overall best response rate of combined CR and CRi/CRp was 44% (four of nine response-evaluable patients). The interim reported results from the IDHIFA® arm of this trial are discussed above under “IDHIFA® - Phase 1(b) frontline combination trial.”

Phase 1/2 frontline combination trial

As discussed above, ivosidenib is being evaluated in a phase 1/2 frontline combination clinical trial, conducted by Celgene, of either IDHIFA® or ivosidenib in combination with VIDAZA® (azacitidine) in newly diagnosed AML patients not eligible for intensive chemotherapy.

In December 2017, we presented interim data from this trial at ASH 2017. As of the September 1, 2017 data cut-off, the median age of patients treated in the ivosidenib arm was 76 (all 65 years old or older), and the most common grade

3-4 hematologic AEs were anemia (18%), febrile neutropenia (18%), neutropenia (9%) and thrombocytopenia (9%), and the most common grade 3-4 non-hematologic AE was pneumonia (18%). IDH differentiation syndrome was reported in one patient. In the ivosidenib arm eight of 11 patients had a response, including four CRs, one CRi, one PR and two MLFSs.

AGILE

Ivosidenib is being evaluated in AGILE, a global, registration-enabling phase 3 clinical trial, combining ivosidenib and VIDAZA® in newly diagnosed AML patients with an IDH1 mutation who are ineligible for intensive chemotherapy. The trial has a primary endpoint of overall survival. The trial is currently open for enrollment and we expect to complete enrollment in 2021.

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Phase 3 frontline combination trial

As discussed above, we plan to support, with Celgene, the initiation of an intergroup sponsored, global, registration-enabling phase 3 trial combining ivosidenib or IDHIFA® and standard induction (7+3) and consolidation chemotherapy with a primary endpoint of event-free survival in frontline AML patients with an IDH1 or IDH2 mutation in the fourth quarter of 2018.

Phase 1 clinical trial (advanced solid tumors)

Ivosidenib 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, cholangiocarcinoma, and chondrosarcoma. 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 once daily.

In June 2017, we reported updated interim data from the dose escalation and dose expansion cohorts of our ongoing phase 1 clinical trial evaluating ivosidenib in patients with IDH1 mutant-positive cholangiocarcinoma at the American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago, Illinois. As of the March 10, 2017 data cut-off, 73 patients with IDH1 mutant positive cholangiocarcinoma had been treated with single agent ivosidenib in the dose escalation (n=24) and expansion cohorts (n=49). Thirteen patients remained on treatment. Ivosidenib was administered at the following dose levels and schedules in the dose-escalation cohort: 100 mg twice daily, and 300, 400, 500, 800 and 1200 mg once a day over a 28 day cycle length. In the dose expansion cohort, patients received 500 mg once a day, which was the selected dose for the ongoing Phase 3 ClarIDHy trial, described below. Among the cholangiocarcinoma population in the trial, the median age is 60 (ranging from 32 to 81). Sixty-five patients had intrahepatic cholangiocarcinoma and eight had extrahepatic disease. The median number of prior systemic therapies was two (ranging from one to five) and 97% of patients received a prior gemcitabine-based chemotherapy regimen. A safety analysis conducted for all 73 treated patients as of the data cut-off demonstrated that ivosidenib was well-tolerated with a favorable safety profile in IDH1 mutant positive cholangiocarcinoma patients. No dose limiting toxicities or treatment-related deaths were observed. The majority of AEs reported were mild to moderate, with the most common regardless of causality being fatigue, nausea, diarrhea and decreased appetite. Four patients experienced drug-related AEs of at least grade 3: two at the 500 mg dose level, fatigue (n=1) and blood alkaline phosphatase increases (n=1), and two at the 1200 mg dose level, fatigue (n=1) and blood phosphorous decreases (n=1). One patient had a dose reduction for a grade 2 AE of worsening leg cramps that was considered to be possibly drug-related. Efficacy data from all 73 treated patients as of the data cut-off showed four patients (5%) experienced a confirmed partial response (one at 300 mg daily and three at 500 mg daily). A partial response is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Forty-one patients (56%) experienced stable disease. Landmark analyses of progression free survival, or PFS, at six and 12 months were 38.5% and 20.7% respectively. The median PFS was 3.8 months (95% CI 3.6, 7.3). Ivosidenib treatment inhibited plasma 2HG to within levels found in healthy volunteers, and also reduced 2HG in tumor biopsies, with 2HG levels in plasma and tumor biopsies showing a positive correlation. Pathology review of on-study tumor biopsies were conducted in a patient achieving a partial response, which showed morphologic changes suggestive of cellular differentiation which is consistent with the proposed mechanism of action of ivosidenib.

In November 2017, we reported updated interim data from the dose expansion cohort of our ongoing phase 1 clinical trial evaluating ivosidenib in patients with progressive low-grade IDH1 mutant-positive glioma at the Society for Neuro-Oncology Annual Meeting in San Francisco, California. As of the May 12, 2017 data cut off, 35 patients (11 from dose escalation, 24 from dose expansion) with non-enhancing glioma had been treated with single agent ivosidenib. Eighteen patients (51%) remained on treatment. Twenty-four patients had World Health Organization (WHO) classified grade 2 tumors, eight had grade 3 tumors, one had a grade 4 tumor and two were unknown. Patients received daily doses of ivosidenib ranging from 300 mg to 900 mg. Twenty-eight patients received a daily dose of 500 mg, which was selected as the expansion dose. The median age of these patients is 38 (ranging from 21 to 71). The

median treatment duration was 16 months (ranging from 1.4 to 27.1 months). The median number of prior therapies was two (ranging from one to five), and the median duration of last systemic therapy was 9.6 months. Sixty-three percent of patients had previously received temozolomide and 57% percent had previously received radiotherapy. A safety analysis conducted for all 35 treated non-enhancing glioma patients as of the data cut-off demonstrated that ivosidenib was well-tolerated with a favorable safety profile in glioma patients. No dose limiting toxicities were observed. The majority of adverse events reported by investigators were mild to moderate, with the most common being headache, diarrhea, nausea and vomiting. There were 5 patients with SAEs and all were deemed unrelated to study treatment. Efficacy data from all 35 non-enhancing glioma patients as of the data cut-off showed that two patients had a minor response by investigator assessment according to the Response Assessment in Neuro-Oncology for low grade glioma (RANO-LGG) and 29 (83%) patients had stable disease. The median PFS for all non-enhancing patients was 13 months, and the median PFS for Grade 2 patients (n=24) had not been reached. For patients in the expansion arm (n=24), the average six-month tumor growth was 24% prior to treatment and 11% following treatment with ivosidenib.

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ClarIDHy

Ivosidenib is being evaluated in ClarIDHy, a registration-enabling phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial of ivosidenib in previously-treated patients with nonresectable or metastatic cholangiocarcinoma with an IDH1 mutation. The trial has an overall endpoint of PFS. The trial was initiated in December 2016 and is currently enrolling patients, and we expect to complete enrollment in 2019.

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 are currently focusing our development efforts for AG-881 in glioma. We and Celgene are developing AG-881 pursuant to the AG-881 Agreements, described below.

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 is 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 receive ascending oral doses of AG-881 to determine the maximum tolerated dose, or MTD, 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 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 enrollment is complete.

We have not yet presented any clinical data from these trials. In October 2017, we presented the first preclinical data of AG-881 in IDH mutant-positive solid and hematologic malignancies at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics in Philadelphia, Pennsylvania.

In the first half of 2018, we intend to initiate a perioperative study with ivosidenib and AG-881 in low grade glioma to further investigate their effects on brain tumor tissue. Pursuant to the AG-881 Agreements, described below, Celgene has elected not to participate in this clinical trial and, as a result, we will fund the trial ourselves. Celgene will continue to co-fund the ongoing phase 1 trials of AG-881 described above.

PKR Activator Program

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 RBCs. 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 RBCs to maintain the production of Adenosine-5’-triphosphate, or ATP, which is a form of chemical energy within cells. Accordingly, total absence of the PKR gene is not compatible with life. PK deficiency leads to a shortened life span for RBCs and is the most common form of non-spherocytic hemolytic anemia in humans.

PK deficiency is a rare genetic disorder and disease understanding is still evolving. We estimate that the prevalence of PK deficiency is between approximately 1-in-75,000 and 1-in-200,000 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 RBCs. 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 RBCs are destroyed in small capillaries or organs and do not spontaneously break open in the circulation. PK deficiency is an autosomal recessive disease whereby all patients inherit two mutations, one from each parent. Children with the disease produce PKR enzyme that has only a fraction of the normal level of activity (generally <50%). Parents of affected children have only one copy of the mutated PKR enzyme and are clinically normal. 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. 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 RBCs. A non-missense mutation is any mutation other than a missense mutation, generally resulting in little functional protein in the RBCs. It is estimated that 58 percent of patients with PK deficiency have two missense mutations, 27 percent have one missense and one non-missense mutation, and 15 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

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of PK deficiency, identify patients and treatment centers, and capture other clinical data, including genetic information. We intend to initiate a global registry for adult and pediatric patients with PK deficiency in the first quarter of 2018 to increase understanding of the long-term disease burden of this chronic anemia.

AG-348: PK Deficiency Program

AG-348 is an orally available small molecule and a potent activator of the wild-type (normal) and mutated PKR enzyme. We have shown that AG-348 can restore ATP levels and decrease 2,3-diphosphoglycerate, or 2,3-DPG, levels in blood sampled from patients with PK deficiency when 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, and provides for potential expansion opportunities into other anemias. The FDA granted us orphan drug designation for AG-348 for treatment of patients with PK deficiency. We intend to initiate two global, pivotal trials of AG-348 in PK deficiency in the first half of 2018: ACTIVATE-T, a single arm trial of approximately 20 regularly transfused patients, is expected to initiate in the first quarter of 2018, and ACTIVATE, a 1:1 randomized, placebo-controlled trial of approximately 80 patients who do not receive regular transfusions, is expected to initiate in the second quarter of 2018. We also expect to initiate a phase 2 proof of concept trial of AG-348 in thalassemia in the fourth quarter of 2018.

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 EHA, establishing proof of concept for AG-348. The trial reached target enrollment of 52 patients in November 2016, and in December 2017, we reported updated data from the trial at ASH 2017. As of the July 14, 2017 data cut-off, 43 patients completed the six-month core dosing period and nine patients discontinued treatment during the core dosing period. Thirty-six of 43 patients who completed the six-month core treatment period entered the extension period. As of the data cut-off, 29 patients remained on treatment in the extension period. A safety analysis was conducted based on all 52 treated patients as of the data cut-off. AG-348 remained well-tolerated, and the majority of treatment-related AEs were Grade 1-2; the most frequent being headache, insomnia and nausea. Four patients experienced treatment-related AEs leading to discontinuation: pleural effusion (n=1), hypertriglyceridemia (n=1), pharyngitis/nausea (n=1) and anemia (n=1). Four patients experienced treatment-related SAEs: withdrawal hemolysis followed by anemia (n=1), anemia (n=1), osteoporosis (n=1) and hypertriglyceridemia (n=1). Measurements of hormone levels in men at doses less than or equal to 50 mg twice daily suggest mild aromatase inhibition by AG-348, and ongoing follow-up will continue to assess the potential clinical significance of this aromatase inhibition. Twenty-six of 52 patients (50%) overall and 25 of 42 patients (60%) with at least one missense mutation achieved rapid 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 Hb increase was 3.4 g/dL (range 1.1 to 5.8 g/dL). The median time to first Hb increase of greater than 1.0 g/dL was 10 days (range 7 to 187 days). The median baseline Hb in patients who experienced a maximum Hb increase of greater than 1.0 g/dL was 9.7 g/dL (range 7.3 to 12.3 g/dL) compared to 8.0 g/dL (range 6.5 to 10.1 g/dL) in patients who did not experience the increase.

ACTIVATE/ACTIVATE-T

We intend to initiate two global, pivotal trials of AG-348 in PK deficiency in the first half of 2018: ACTIVATE-T, a single arm trial of approximately 20 regularly transfused patients, is expected to initiate in the first quarter of 2018, and ACTIVATE, a 1:1 randomized, placebo-controlled trial of 80 patients who do not receive regular transfusions, is expected to initiate in the second quarter of 2018. The primary endpoint of the ACTIVATE trial is the proportion of patients who achieve at least a 1.5 g/dL increase in Hb sustained over multiple visits, and the primary endpoint of the ACTIVATE-T trial is a reduction in transfusion burden over a six-month period compared to the patient's transfusion history.

In addition to the above planned and ongoing clinical trials of AG-348, we plan to initiate a phase 2 proof of concept trial of AG-348 in thalassemia in the fourth quarter of 2018.

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-270: Targeting MAT2A for the treatment of MTAP-deleted cancers

AG-270, a MAT2A inhibitor, is our development candidate focused on MTAP-deleted cancers. We submitted an IND for AG-270 in November 2017 and, in December 2017, the FDA concluded that we may proceed with a proposed phase 1 dose-escalation trial in multiple tumor types carrying an MTAP deletion, which we expect to initiate in the first quarter of 2018.

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MTAP is a metabolic gene that is deleted in approximately 15 percent of all cancers. We have shown in preclinical studies that MTAP deletion predicts sensitivity to inhibition of a subset of enzymes involved in the synthesis or utilization of the methyl donor S-adenosylmethionine, or SAM. Among this subset of enzymes, we have targeted MAT2A, the enzyme responsible for
the synthesis of SAM in tumor cells. We have discovered small molecule inhibitors of MAT2A, including AG-270, that reduce SAM production and cause antiproliferative effects in MTAP-null cancer cell lines in vitro and in MTAP-deleted tumor models in vivo. MTAP deletion is readily detected by a genomic or immunohistochemistry test, thus allowing the selection of patients predicted to be sensitive to the therapy.

In March 2017, we announced that Celgene designated AG-270 as a development candidate under our 2016 research agreement with Celgene, or the 2016 Agreement. Pursuant to the 2016 Agreement, Celgene paid us an $8.0 million designation fee upon its designation of AG-270 as a development candidate. Exploratory research, drug discovery and early development of AG-270 is led by us, and Celgene will have an opt-in right on AG-270 up through phase 1 dose escalation for at least a $30.0 million fee. Upon opt-in, we and Celgene will have global co-development and co-commercialization rights with a worldwide 50/50 cost and profit share on AG-270, and we will be eligible for up to $168.8 million in clinical and regulatory milestone payments.

Targeting DHODH for the treatment of hematologic malignancies

In January 2018, we announced that we plan to submit an IND in the fourth quarter of 2018 for our latest development candidate, an inhibitor of DHODH, licensed by us from Aurigene Discovery Technologies Limited, for the treatment of hematologic malignancies. We have discovered a lineage-specific dependence on DHODH in hematologic malignancies, particularly AML and diffuse large B-cell lymphoma. DHODH catalyzes a critical step in the biosynthesis of pyridimidines, which are critical for the production of RNA and DNA. We believe that DHODH inhibition will be differentiated from standard-of-care therapies, both by exhibiting activity in cancers that are resistant to standard-of-care chemotherapeutics and through a mechanism of anti-tumor effect that combines cell growth arrest and cellular differentiation.

Collaborations with Celgene

2016 Agreement

In May 2016, we entered into the 2016 Agreement with Celgene, which is focused on MIO. In addition to new programs identified under the 2016 Agreement, both parties also agreed that all future development and commercialization of two remaining cancer metabolism programs discovered under the 2010 Agreement, including AG-270, our MAT2A inhibitor, will 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, and 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 preclinical and clinical development for such program through the 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. We may conduct further research and preclinical and clinical development activities on any continuation program, at our expense, through the completion of an initial phase 1 dose escalation study.

We granted Celgene the right to obtain exclusive options for 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: (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 two parties

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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 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 than the 65/35 program, we and Celgene 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 party 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 in the I&I field.

Financial terms Under the terms of the 2016 Agreement, we 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. During the year ended December 31, 2017, we received $8.0 million from Celgene upon the designation of AG-270, our MAT2A inhibitor, as a development candidate. 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.

We are eligible to receive the following milestone-based payments associated with the 2016 Agreement:

Program	Milestone	Amount
65/35 program in IO field	Specified clinical development event	$25.0 million
65/35 program in IO field	Specified regulatory milestone events	Up to $183.8 million
50/50 program in IO field	Specified clinical development event	$20.0 million
50/50 program in IO field	Specified regulatory milestone events	Up to $148.8 million
I&I field	Specified clinical development event	$25.0 million
I&I field	Specified regulatory milestone events	Up to $236.3 million
I&I field	Specified commercial milestone events	Up to $125.0 million

Additionally, 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.

Opt-out right Under the 2016 Agreement, we 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.

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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.

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 or 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.

Ivosidenib Letter Agreement

On May 17, 2016, we entered into a letter agreement with Celgene regarding ivosidenib, or the Ivosidenib Letter Agreement. Under the Ivosidenib Letter Agreement, 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 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 Ivosidenib Letter Agreement, we obtained global rights to ivosidenib and the IDH1 program. Neither party will have any further financial obligation, including royalties or milestone payments, to the other concerning ivosidenib or the IDH1 program. Under the terms of the Ivosidenib Letter Agreement, the parties also agreed to conduct specified transitional activities in connection with the termination. In addition, pursuant to the Ivosidenib Letter Agreement, the parties are released from their exclusivity obligations under the 2010 Agreement with respect to the IDH1 program. The Ivosidenib 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, we entered into a joint worldwide development and profit share collaboration and license agreement with Celgene, and our wholly owned subsidiary, Agios International Sarl, 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 joint worldwide collaboration focused on the development and commercialization of AG-881 products. Under the terms of the AG-881 Agreements, we received an initial upfront payment of $10.0 million in May 2015 and are eligible to receive milestone-based payments. The parties will split all worldwide development costs equally, subject to specified exceptions, as well as any profits from any net sales of, or commercialization losses related to, licensed AG-881 products. Either party may, at its own expense and with the other party's permission, undertake additional development activities outside of the scope of the development plan agreed upon with the other party.

Financial terms We are eligible to receive up to $70.0 million in potential milestone payments under the AG-881 Agreements. The potential milestone payments are comprised of: (i) a $15.0 million milestone payment for filing of

the 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-double digit to mid-teen percentage rates on net sales if we elect not to 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

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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.

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 in their entirety for any reason upon ninety days written notice to us. Either party may terminate the AG-881 Agreements for the insolvency of the other party. Either party may terminate the AG-881 Agreements in their entirety or with respect to one of the agreements upon 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 AG-881 Agreements. 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

In April 2010, we entered into a collaboration agreement with Celgene focused on cancer metabolism, or 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 our 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 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 is the lead development candidate, the sole program remaining under the 2010 Agreement is IDHIFA®, a co-commercialized licensed program for which Celgene leads and funds global development and commercialization activities. We have exercised our right to participate in a portion of commercialization activities in the United States for IDHIFA® in accordance with the applicable commercialization plan.

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, 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 remaining terms of the 2010 Agreement, we are eligible to receive up to $95.0 million in potential milestone payments for the IDHIFA® program. The potential milestone payments are comprised of: (i) up to $70.0 million in milestone payments upon achievement of specified ex-U.S. regulatory milestone events, and (ii) a $25.0 million milestone payment upon achievement of a specified commercial milestone event.

Under the 2010 Agreement, we may also receive royalties at tiered, low-double digit to mid-teen percentage rates on net sales of IDHIFA®. Assuming all other revenue recognition criteria are met, royalty payments will be recognized

as revenue in the period in which they are earned. During the year ended December 31, 2017, we earned $1.9 million in royalty revenue under the 2010 Agreement.

Termination. Unless terminated earlier by either party, the term of the 2010 Agreement will continue until the expiration of all royalty terms with respect to IDHIFA®. Celgene may terminate the 2010 Agreement for convenience in its entirety or with respect to IDHIFA® upon ninety days written notice to us. Either we or Celgene may terminate the 2010 Agreement, in its entirety or with respect to IDHIFA®, 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.

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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 IDHIFA® 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 IDHIFA® 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. 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 IDHIFA®, ivosidenib, AG-881, AG-348 and AG-270, 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 January 31, 2018 we owned or licensed approximately 16 issued U.S. patents, 26 pending U.S. patent applications, 75 issued foreign patents, 327 pending foreign patent applications, and 12 pending Patent Cooperation Treaty, or PCT, patent applications directed to our key product candidates. The foreign issued patents and patent applications are in a number of jurisdictions, including Argentina, Australia, Austria, Belgium, Brazil, Canada, China, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Japan, Lithuania, Mexico, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom.
The intellectual property portfolios for our most advanced programs as of January 31, 2018 are summarized below. Prosecution is a lengthy process, during which the scope of the claims initially submitted for examination by the U.S. Patent and Trademark Office, or USPTO, can be significantly narrowed by the time they issue, if they issue at all. We expect this could be the case with respect to some of our pending patent applications referred to below.

IDH mutant inhibitor programs

The intellectual property portfolio for our IDH mutant inhibitor programs contains patent applications directed to compositions of matter for IDHIFA®, ivosidenib, and AG-881, as well as analogs thereof, and compositions of matter for IDH mutant inhibitors with different compound families, as well as methods of use for these novel compounds and diagnostic methods for detecting various IDH1 and IDH2 mutations. As of January 31, 2018, we owned approximately 10 issued U.S. patents, 10 issued foreign patents, 20 pending U.S. patent applications, 270 pending foreign patent applications in a number of jurisdictions, and 10 pending PCT patent applications directed to our IDH mutant product candidates. The patents that have issued or will issue for our IDH mutant product candidates will have a statutory expiration date of at least 2033 to 2034. Patent term adjustments or patent term extensions could result in later expiration dates.

PK deficiency program

The intellectual property portfolio for our PK deficiency program contains patent applications directed to compositions of matter for AG-348, as well as analogs thereof, and compositions of matter for PKR activators with different compound families, as well as methods of use for these novel compounds. As of January 31, 2018, we owned approximately six issued U.S. patents, 65 issued foreign patents, five pending U.S. patent applications and 55 pending foreign patent applications in a number of jurisdictions directed to our PK deficiency program, including our product candidate. The patents that have issued or will issue for our PK deficiency program will have a statutory expiration

date of at least 2030. Patent term adjustments or patent term extensions could result in later expiration dates.

MTAP-deleted cancer program

The intellectual property portfolio for our MTAP-deleted cancer program contains patent applications directed to compositions of matter for AG-270, as well as analogs thereof and other compound families, as well as methods of use for these novel compounds and diagnostic methods for detecting MTAP deletions. As of January 31, 2018, we owned approximately one pending U.S. patent application, two pending foreign patent applications, and two pending PCT patent applications directed to

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our MTAP-deleted cancer program. The patents that would issue for our MTAP-deleted cancer program will have a statutory expiration date of at least 2037. Patent term adjustments or patent term extensions could result in later expiration dates.

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 USPTO in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier filed patent. The term of a patent that covers a drug or biological product may also be eligible for patent term extension when FDA approval is granted, provided statutory and regulatory requirements are met. In the future, if and when our product candidates receive approval by the FDA or foreign regulatory authorities, we expect to apply for patent term extensions on issued patents covering those products, depending upon the length of the clinical trials for each medicine and other factors. There can be no assurance that any of our pending patent applications will issue or that we will benefit from any patent term extension or favorable adjustment to the term of any of our patents.

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

In addition to patents, we rely upon unpatented trade secrets and know-how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our proprietary information, in part, using confidentiality agreements with our collaborators, scientific advisors, employees and consultants, and invention assignment agreements with our employees. We also have agreements requiring assignment of inventions with selected consultants, scientific advisors and collaborators. The confidentiality agreements are designed to protect our proprietary information and, in the case of agreements or clauses requiring invention assignment, to grant us ownership of technologies that are developed through a relationship with a third party.

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

Competition

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

We compete in the segments of the pharmaceutical, biotechnology and other related markets that address cancer metabolism, 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, or Bayer; Calithera Biosciences; Cornerstone Pharmaceuticals, Inc.; Daiichi Sankyo Company, Ltd., or Daiichi Sankyo; 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, Bayer, Daiichi Sankyo and Forma are conducting phase 1 clinical trials of their IDH mutant inhibitors, BAY1436032, DS-1001b and FT-2102, respectively, in patients with hematologic and solid tumors, including AML, MDS and glioma. 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

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

In addition to currently marketed therapies, there are also a number of medicines in late stage clinical development to treat cancer, including immuno-oncology 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. For example, several investigators have reported that IDH mutant AML and glioma are sensitive to poly (ADP-ribose) polymerase inhibition in cell culture and animal models. In the MIO field, our principal competitors include AstraZeneca PLC, Merck, Genentech, Bristol-Myers Squibb Company and Novartis.

Rare genetic diseases. In the field of RGDs, our principal competitors include Alexion Pharmaceuticals, Inc.; BioMarin Pharmaceutical, Inc.; Genzyme Corporation, a Sanofi company; and Shire Plc. In addition, Rocket Pharma LTD is in the preclinical stages of development of a gene therapy to treat patients with PK deficiency.

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

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

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

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

Manufacturing

We do not own or operate, and currently have no plans to establish, any manufacturing facilities. We currently rely, and expect to continue to rely, on third parties for the manufacture of our product candidates for preclinical and clinical testing, as well as for commercial manufacture of any products that we may commercialize. To date, we have obtained materials for IDHIFA®, ivosidenib, AG-881, AG-348, and AG-270 for our ongoing and planned clinical testing from third-party manufacturers. Although we have long-term supply arrangements in place for the commercial supply of ivosidenib, we primarily obtain our

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supplies from these manufacturers on a purchase order basis. We do not currently have arrangements in place for redundant supply for bulk drug substance and drug product. As we have done for ivosidenib, for all of our other 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.

IDHIFA®, ivosidenib, AG-881, AG-348, and AG-270 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, 2017, 2016 and 2015, company-sponsored research and development expenses were $292.7 million, $220.2 million, and $141.8 million, respectively.

Review and Approval of Drugs in the United States

In the United States, the FDA regulates drug products under the Federal Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. The failure to comply with applicable requirements under the FDCA and other 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.

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 an NDA;
- review of the product 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 Risk Evaluation and Mitigation Strategies, or REMS, and post approval studies required by the FDA.

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Preclinical studies

Preclinical studies include laboratory evaluation of the purity and stability of the manufactured drug substance or active pharmaceutical ingredient and the formulated drug or drug product, as well as in vitro and animal studies to assess the 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.

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

The IND and IRB processes

An IND is an exemption from the FDCA that allows an unapproved drug to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer an investigational drug to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug that is not the subject of an approved NDA. In support of a request for an IND, applicants must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, 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. The FDA requires a 30 day waiting period after the filing of each IND before clinical trials may begin. This waiting period is designed to allow the FDA to review the IND to determine whether human research subjects will be exposed to unreasonable health risks. At any time during this 30 day period, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin.

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial 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.

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 certain FDA 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 IND as support for an IND or an NDA. 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.

In addition to the foregoing IND requirements, 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. 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 product candidate has been associated with unexpected serious harm to patients.

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee or DSMB. This group provides authorization for whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the study. Suspension

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or termination of development during any phase of clinical trials can occur if it is determined that the participants or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by us based on evolving business objectives and/or competitive climate.

Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on its ClinicalTrials.gov website.

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.

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

- Phase 1. The drug is initially introduced into healthy human subjects or, in certain indications such as cancer, patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness 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. 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.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if SAEs 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. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution, 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.

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.

Submission of an NDA to 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 subject to an application user fee, which for federal fiscal year 2018 is $2,421,495 for an application requiring clinical data. The sponsor of an approved NDA is also subject to a program fee for fiscal year 2018 of $304,162. 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.

The FDA conducts a preliminary review of an NDA within 60 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

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the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in depth substantive review. The FDA has agreed to certain performance goals in the review process of NDAs. Most such applications are meant to be reviewed within ten months from the date of filing, and most applications for "priority review" products are meant to be reviewed within six months of filing. The review process 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 (such as 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. The FDA must implement a protocol to expedite review of responses to inspection reports pertaining to certain drug applications, including applications for drugs in a shortage or drugs for which approval is dependent on remediation of conditions identified in the inspection report.

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 may 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, priority review and regenerative advanced therapy 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 referred to as fast track designation, breakthrough therapy designation, priority review designation and regenerative advanced therapy designation.

Specifically, 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.

Second, 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

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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.

Finally, with passage of the 21st Century Cures Act, or Cures Act, in December 2016, Congress authorized the FDA to accelerate review and approval of products designated as regenerative advanced therapies. A product is eligible for this designation if it is a regenerative medicine therapy (as defined in the Cures Act) that is intended to treat, modify, reverse or cure a serious or life threatening disease or condition and preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition. The benefits of a regenerative advanced therapy designation include early interactions with FDA to expedite development and review, benefits available to breakthrough therapies, potential eligibility for priority review and accelerated approval based on surrogate or intermediate endpoints.

Accelerated approval pathway

The FDA may grant accelerated approval to a drug for a serious or life threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the drug 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. Drugs 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 drug, such as an effect on IMM. The FDA has limited 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 drug.

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 drug, 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 drugs 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 drug's clinical benefit. As a result, a drug candidate approved on this basis is subject to rigorous post marketing compliance requirements, including the completion of Phase 4 or post approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post approval studies, or confirm a clinical benefit during post marketing studies, would allow the FDA to withdraw the drug from the market on an expedited basis. All promotional materials for drug candidates approved under accelerated regulations are subject to prior review by the FDA.

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

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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 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, 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 the marketing, labeling, advertising and promotion of prescription drug products placed on the market. This regulation includes, among other things, standards and regulations for direct-to-consumer advertising, communications regarding unapproved uses, industry-sponsored scientific and educational activities, and promotional activities involving the Internet and social media. Promotional claims about a drug's safety or effectiveness are prohibited before the drug is approved. After approval, a drug product generally may not be promoted for uses that are not approved by the FDA, as reflected in the product's prescribing information. In the United States, healthcare professionals are generally permitted to prescribe drugs for such uses not described in the drug's labeling, known as off-label uses, because the FDA does not regulate the practice of medicine. However, FDA regulations impose rigorous restrictions on manufacturers' communications, prohibiting the promotion of off-label uses. It may be permissible, under very specific, narrow conditions, for a manufacturer to engage in nonpromotional, non-misleading communications regarding off-label information, such as distributing scientific or medical journal information. If a company is found to have promoted off-label uses, it may become subject to adverse public relations and administrative and judicial enforcement by the FDA, the Department of Justice, or the Office of the Inspector General of the Department of Health and Human Services, as well as state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that

materially restrict the manner in which a company promotes or distributes drug products. The federal government has levied large civil and criminal fines against companies for alleged improper promotion, and has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, and its implementation regulations, as well as the Drug Supply Chain Security Act, or DSCSA, which regulates the distribution of and tracing of prescription drugs and prescription drug samples at the federal level, and sets 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 DSCSA imposes requirements to ensure accountability in distribution and to identify and remove counterfeit and other illegitimate products from the market.

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Section 505(b)(2) NDAs

NDAs for most new drug products are based on two full clinical studies which must contain substantial evidence of the safety and efficacy of the proposed new product. These applications are submitted under Section 505(b)(1) of the FDCA. The FDA is, however, authorized to approve an alternative type of NDA under Section 505(b)(2) of the FDCA. This type of application allows the applicant to rely, in part, on the FDA's previous findings of safety and efficacy for a similar product, or published literature. Specifically, Section 505(b)(2) applies to NDAs for a drug for which the investigations made to show whether or not the drug is safe for use and effective in use and relied upon by the applicant for approval of the application "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted."

Thus, Section 505(b)(2) authorizes the FDA to approve an NDA based on safety and effectiveness data that were not developed by the applicant. NDAs filed under Section 505(b)(2) may provide an alternate and potentially more expeditious pathway to FDA approval for new or improved formulations or new uses of previously approved products. If the Section 505(b)(2) applicant can establish that reliance on the FDA's previous approval is scientifically appropriate, the applicant 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 to support the change from the approved product. The FDA may then approve the new drug candidate for all or some of the label indications for which the referenced product has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant.

Abbreviated new drug applications for generic drugs

In 1984, with passage of the Hatch Waxman Amendments to the FDCA, Congress authorized the FDA to approve generic drugs that are the same as drugs previously approved by the FDA under the NDA provisions of the statute. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the agency. 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.

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, and the strength 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. Clinicians 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 clinicians 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.

The FDA must establish a priority review track for certain generic drugs, requiring the FDA to review a drug application within eight (8) months for a drug that has three (3) or fewer approved drugs listed in the Orange Book and is no longer protected by any patent or regulatory exclusivities, or is on the FDA's drug shortage list. The new legislation also authorizes the FDA to expedite review of ''competitor generic therapies'' or drugs with inadequate generic competition, including holding meetings with or providing advice to the drug sponsor prior to submission of the application.

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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 applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would.

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 ANDA 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 ANDA applicant is not seeking approval).

If the ANDA 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 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 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 ANDA applicant.

To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would. As a result, approval of a Section 505(b)(2) NDA can be stalled until all the listed patents claiming the referenced product have expired, until any non patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, listed in the Orange Book for the referenced product has expired, and, in the case of a Paragraph IV certification and subsequent patent infringement suit, until the earlier of 30 months, settlement of the lawsuit or a decision in the infringement case that is favorable to the Section 505(b)(2) applicant.

Pediatric studies and exclusivity

Under the Pediatric Research Equity Act of 2003, 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 the Food and Drug Administration Safety and Innovation Act or FDASIA, in 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 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. For drugs intended to treat a serious or life-threatening disease or condition, the FDA must, upon the request of an applicant, meet to discuss preparation of the initial pediatric study plan or to discuss deferral or waiver of pediatric assessments. In addition, the FDA will meet early in the development process to discuss pediatric study plans with drug sponsors. The legislation requires the FDA to meet with drug sponsors by no later than the end-of-phase 1 meeting for serious or life-threatening diseases and by no later than ninety (90) days after the FDA's receipt of the study plan.

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 otherwise required by regulation, 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

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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. 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 a generic (ANDA or 505(b)(2) NDA) 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 a proposed generic 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 product designation before submitting an NDA. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product with orphan status 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 be receiving orphan product exclusivity. Orphan product exclusivity means that the FDA may not approve any other applications for the same product for the same indication for seven years, except in certain limited circumstances. Competitors may receive approval of different products for the indication for which the orphan product has exclusivity and may obtain approval for the same product but for a different indication. If a drug or drug product designated as an orphan product ultimately receives marketing approval for an indication broader than what was designated in its orphan product application, it may not be entitled to exclusivity.

Orphan drug exclusivity will not bar approval of another orphan drug 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. The new legislation reverses prior precedent holding that the Orphan Drug Act unambiguously required the FDA to recognize orphan exclusivity regardless of a showing of clinical superiority.

Patent term restoration and extension

A patent claiming a new drug product may be eligible for a limited patent term extension 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. 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 restoration 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 USPTO reviews and approves the application for any patent term extension or restoration in consultation with the FDA. We cannot provide any assurance that any patent term extension with respect to any U.S. patent will be obtained and, if obtained, the duration of such extension, in connection with any of our product candidates.

The 21st Century Cures Act

On December 13, 2016, President Obama signed the 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 increased funding for the FDA to spend on innovation projects. The new law also amends the Public Health Service Act to reauthorize and expand funding for the

NIH. 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 the 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 Public Health Service Act, or 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, the Cures Act reauthorizes the existing priority review voucher program for certain drugs intended to treat rare pediatric diseases until 2020; creates a new priority review voucher program for drug applications determined to be material national security

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threat medical countermeasure applications; revises the FDCA to streamline review of combination product applications; requires the 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 the FDA to designate a drug as a "regenerative advanced therapy," thereby making it eligible for certain expedited review and approval designations.

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.

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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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 Drug Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, the company would need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. The approval process ultimately varies between countries and jurisdictions and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries and jurisdictions might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country or jurisdiction does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country or jurisdiction may negatively impact the regulatory process in others.

Procedures governing approval of drug products in the European Union

Pursuant to the European Clinical Trials Directive, a system for the approval of clinical trials in the E.U. has been implemented through national legislation of the member states. Under this system, an applicant must obtain approval from the competent national authority of a E.U. member state in which the clinical trial is to be conducted. Furthermore, the applicant may only start a clinical trial after a competent ethics committee has issued a favorable opinion. A clinical trial application, or CTA, must be accompanied by an investigational medicinal product dossier, or IMPD, with supporting information prescribed by the European Clinical Trials Directive and corresponding national laws of the member states and further detailed in applicable guidance documents.

To obtain marketing approval of a product under E.U. regulatory systems, an applicant must submit an MAA either under a centralized or decentralized procedure. The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all E.U. member states. The centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional.

Under the centralized procedure, the Committee for Medicinal Products for Human Use, or the CHMP, established at the EMA is responsible for conducting the initial assessment of a product. The CHMP is also responsible for several post authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the E.U., the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. In this circumstance, the EMA ensures that the opinion of the CHMP is given within 150 days.

The decentralized procedure is available to applicants who wish to market a product in various E.U. member states where such product has not received marketing approval in any E.U. member states before. The decentralized procedure provides for approval by one or more other, or concerned, member states of an assessment of an application performed by one member state designated by the applicant, known as the reference member state. Under this procedure, an applicant submits an application based on identical dossiers and related materials, including a draft summary of product characteristics, and draft labeling and package leaflet, to the reference member state and concerned member states. The reference member state prepares a draft assessment report and drafts of the related materials within 210 days after receipt of a valid application. Within 90 days of receiving the reference member state's assessment report and related materials, each concerned member state must decide whether to approve the assessment

report and related materials.

If a member state cannot approve the assessment report and related materials on the grounds of potential serious risk to public health, the disputed points are subject to a dispute resolution mechanism and may eventually be referred to the European Commission, whose decision is binding on all member states.

Within this framework, manufacturers may seek approval of hybrid medicinal products under Article 10(3) of Directive 2001/83/EC. Hybrid applications rely, in part, on information and data from a reference product and new data from appropriate preclinical tests and clinical trials. Such applications are necessary when the proposed product does not meet the strict definition of a generic medicinal product, or bioavailability studies cannot be used to demonstrate bioequivalence, or there are

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changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference medicinal product. In such cases the results of tests and trials must be consistent with the data content standards required in the Annex to the Directive 2001/83/EC, as amended by Directive 2003/63/EC.

Hybrid medicinal product applications have automatic access to the centralized procedure when the reference product was authorized for marketing via that procedure. Where the reference product was authorized via the decentralized procedure, a hybrid application may be accepted for consideration under the centralized procedure if the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation, or the granting of a community authorization for the medicinal product is in the interest of patients at the community level.

Clinical trial approval in the European Union

Requirements for the conduct of clinical trials in the E.U. including GCP are set forth in the Clinical Trials Directive 2001/20/EC and the GCP Directive 2005/28/EC. Pursuant to Directive 2001/20/EC and Directive 2005/28/EC, as amended, a system for the approval of clinical trials in the E.U. has been implemented through national legislation of the E.U. member states. Under this system, approval must be obtained from the competent national authority of each E.U. member state in which a study is planned to be conducted. To this end, a CTA is submitted, which must be supported by an IMPD and further supporting information prescribed by Directive 2001/20/EC and Directive 2005/28/EC and other applicable guidance documents. Furthermore, a clinical trial may only be started after a competent ethics committee has issued a favorable opinion on the CTA in that country.

In April 2014, the E.U. passed the new Clinical Trials Regulation, (EU) No 536/2014, which will replace the current Clinical Trials Directive 2001/20/EC. To ensure that the rules for clinical trials are identical throughout the E.U., the new E.U. clinical trials legislation was passed as a regulation that is directly applicable in all E.U. member states. All clinical trials performed in the E.U. are required to be conducted in accordance with the Clinical Trials Directive 2001/20/EC until the new Clinical Trials Regulation (EU) No 536/2014 becomes applicable. According to the current plans of the EMA, the new Clinical Trials Regulation will become applicable in 2019. The Clinical Trials Directive 2001/20/EC will, however, still apply three years from the date of entry into application of the Clinical Trials Regulation to (i) clinical trials applications submitted before the entry into application and (ii) clinical trials applications submitted within one year after the entry into application if the sponsor opts for old system.

The new Clinical Trials Regulation aims to simplify and streamline the approval of clinical trial in the E.U. The main characteristics of the regulation include: a streamlined application procedure via a single entry point, the E.U. portal; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures that will spare sponsors from submitting broadly identical information separately to various bodies and different member states; a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts (Part I is assessed jointly by all member states concerned, and Part II is assessed separately by each member state concerned); strictly defined deadlines for the assessment of CTAs; and the involvement of the ethics committees in the assessment procedure in accordance with the national law of the member state concerned but within the overall timelines defined by the Clinical Trials Regulation.

Periods of authorization and renewals

Marketing authorization is valid for five years in principle and the marketing authorization may be renewed after five years on the basis of a re evaluation of the risk benefit balance by the EMA or by the competent authority of the authorizing member state. To this end, the marketing authorization holder must provide the EMA or the competent authority 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 unlimited period, unless the European Commission or the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five year renewal. Any authorization which is not followed by the actual placing of the drug on the E.U. market (in case of centralized procedure) or on the market of the authorizing member state within three years after authorization ceases to be valid (the so called sunset clause).

Data and market exclusivity in the European Union

In the E.U., new chemical entities qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. This data exclusivity, if granted, prevents regulatory authorities in the E.U. from referencing the innovator's data to assess a generic (abbreviated) application for eight years, after which generic marketing authorization can be submitted, and the innovator's data may be referenced, but not approved for two years. 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 their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity and the sponsor is able to gain the prescribed period of data exclusivity, another

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company nevertheless could also market another version of the product if such company can complete a full MAA with a complete database of pharmaceutical test, preclinical tests and clinical trials and obtain marketing approval of its product.

Orphan drug designation and exclusivity

Regulation 141/2000 provides that a drug shall be designated as an orphan drug if its sponsor can establish: that the product is intended for the diagnosis, prevention or treatment of a life threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the European Community when the application is made, or that the product is intended for the diagnosis, prevention or treatment of a life threatening, seriously debilitating or serious and chronic condition in the European Community and that without incentives it is unlikely that the marketing of the drug in the European Community would generate sufficient return to justify the necessary investment. 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 Community or, if such method exists, the drug will be of significant benefit to those affected by that condition.

Regulation 847/2000 sets out criteria and procedures governing designation of orphan drugs in the E.U. Specifically, an application for designation as an orphan product can be made any time prior to the filing of an application for approval to market the product. Marketing authorization for an orphan drug leads to a ten year period of market exclusivity. This period may, however, be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan drug designation, for example because the product is sufficiently profitable not to justify market exclusivity. Market exclusivity can be revoked only in very selected cases, such as consent from the marketing authorization holder, inability to supply sufficient quantities of the product, demonstration of “clinically relevant superiority” by a similar medicinal product, or, after a review by the Committee for Orphan Medicinal Products, requested by a member state in the fifth year of the marketing exclusivity period (if the designation criteria are believed to no longer apply). Medicinal products designated as orphan drugs pursuant to Regulation 141/2000 shall be eligible for incentives made available by the European Community and by the member states to support research into, and the development and availability of, orphan drugs.

Regulatory requirements after marketing authorization

As in 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 E.U. Member States both before and after grant of the manufacturing and marketing authorizations. The holder of an E.U. marketing authorization for a medicinal product must, for example, comply with E.U. 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. The manufacturing process for medicinal products in the E.U. is also 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 E.U. laws, including compliance with E.U. cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients.

In the E.U., the advertising and promotion of approved products are subject to E.U. Member States’ laws governing promotion of medicinal products, interactions with clinicians, misleading and comparative advertising and unfair commercial practices. In addition, other legislation adopted by individual E.U. 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, which is prohibited in the European Union.

Brexit and the regulatory framework in the United Kingdom

On June 23, 2016, the electorate in the United Kingdom, or U.K. voted in favor of leaving the E.U, which is commonly referred to as “Brexit”. Thereafter, on March 29, 2017, the country formally notified the E.U. of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. The withdrawal of the U.K. from the E.U. will take effect either on the effective date of the withdrawal agreement or, in the absence of agreement, two years after the U.K. provides a notice of withdrawal pursuant to the E.U. Treaty. Since the regulatory framework for pharmaceutical

products in the U.K. covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from E.U. directives and regulations, Brexit could materially impact the future regulatory regime which applies to products and the approval of product candidates in the U.K. It remains to be seen how, if at all, Brexit will impact regulatory requirements for product candidates and products in the U.K.

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Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Sales of 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, or 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 regulatory approvals. Nonetheless, product candidates may not be considered medically necessary or cost effective. Additionally, a payor's decision to provide coverage for a drug 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 for the drug product. Third party reimbursement may not be sufficient to maintain price levels high enough to realize an appropriate return on 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 regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Outside the United States, ensuring adequate coverage and payment for our product candidates 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 candidates 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 E.U., pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost effectiveness of a particular drug candidate to currently available therapies. For example, the E.U. provides options for its member states to restrict the range of drug products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. E.U. member states may approve a specific price for a drug product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the drug product on the market. Other member states allow companies to fix their own prices for drug products, but monitor and control company profits. The downward pressure on healthcare costs in general, particularly prescription drugs, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross border imports from low priced markets exert competitive pressure that may reduce pricing within a country. Any country that has price controls or reimbursement limitations for drug products may not allow favorable reimbursement and pricing arrangements.

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 regulatory approval. Arrangements with providers, consultants, third party payors and customers are subject to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain our business and/or financial arrangements. Such restrictions under applicable federal and state healthcare laws and regulations, include the following:

- the federal Anti Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;

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- 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 or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal laws that prohibit, among other things, knowingly and willingly executing, or attempting to execute, 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, which also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- 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 U.S. Department of Health and Human Services, information related to payments and other transfers of value to clinicians and teaching hospitals and clinician ownership and investment interests; 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 clinicians 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.

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;
- 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

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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 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 will stay in effect through 2024 unless additional Congressional action is taken, and the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several types of 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 otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Further, there have been several recent U.S. congressional inquiries and proposed state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products.

These healthcare reforms, 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 for any approved product and/or the level of reimbursement physicians receive for administering any approved product. Reductions in reimbursement levels may negatively impact the prices or the frequency with which products are prescribed or administered. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. Since enactment of the ACA, there have been numerous legal challenges and Congressional actions to repeal and replace provisions of the law. In May 2017, the U.S. House of Representatives passed legislation known as the American Health Care Act of 2017. Thereafter, the Senate Republicans introduced and then updated a bill to replace the ACA known as the Better Care Reconciliation Act of 2017. The Senate Republicans also introduced legislation to repeal the ACA without companion legislation to replace it, and a "skinny" version of the Better Care Reconciliation Act of 2017. In addition, the Senate considered proposed healthcare reform legislation known as the Graham-Cassidy bill. None of these measures was passed by the U.S. Senate.

The Trump Administration has also taken executive actions to undermine or delay implementation of the ACA. In January 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. In October 2017, the President signed a second Executive Order allowing for the use of association health plans and short-term health insurance, which may provide fewer health benefits than the plans sold through the ACA exchanges. At the same time, the Administration announced that it will discontinue the payment of cost-sharing reduction, or CSR, payments to insurance companies until Congress approves the appropriation of funds for such CSR payments. The loss of the CSR payments is expected to increase premiums on certain policies issued by qualified health plans under the ACA. A bipartisan bill to appropriate funds for CSR payments was introduced in the Senate, but the future of that bill is uncertain.

More recently, with enactment of the Tax Cuts and Jobs Act of 2017, which was signed by the President on December 22, 2017, Congress repealed the “individual mandate.” The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, will become effective in 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise.

Further, each chamber of the Congress has put forth multiple bills designed to repeal or repeal and replace portions of the ACA. Although none of these measures has been enacted by Congress to date, Congress may consider other legislation to repeal and replace elements of the ACA. The Congress will likely consider other legislation to replace elements of the ACA, during the next Congressional session.

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Segment Reporting and Geographical Information

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. For segment and geographical financial information, see Note 2, Summary of Significant Accounting Policies, to the financial statements appearing elsewhere in this Annual Report on Form 10-K, which are incorporated herein by reference.

Our Scientific Founders and Advisors

Founders

Our founders 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. Dr. Cantley is a foremost expert in understanding the biochemical pathways linking cancer and energy metabolism.

Tak W. Mak, Ph.D. Dr. Mak is professor of medical biophysics, University of Toronto; director of the Advanced Medical Discovery Institute; and director of the Campbell Family Institute for Breast Cancer Research. Dr. Mak is a preeminent researcher of the biology of the immune system, the biology of apoptosis and the pathogenesis of cancer.

Craig B. Thompson, M.D. Dr. Thompson is president and CEO of Memorial Sloan-Kettering Cancer Center. Dr. Thompson is an authority in the study of how genes regulate apoptosis and metabolism and investigates their application in treating cancer.

Scientific Advisors

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

Name	Primary affiliation
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
Ralph Deberardinis, M.D., Ph.D.	Children's Medical Center Research Institute at University of Texas Southwestern
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
Craig B. Thompson, M.D.	Memorial Sloan-Kettering Cancer Center
Matthew Vander Heiden, M.D., Ph.D.	Koch Institute for Integrative Cancer Research at Massachusetts Institute of Technology

Employees

As of December 31, 2017, we had 382 full-time employees, including 132 employees with M.D. or Ph.D. degrees. Of these full-time employees, 274 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. 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.

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Available Information

Our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and any amendments to these reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, are available free of charge on our website located at www.agios.com as soon as reasonably practicable after they are filed with or furnished to the Securities and Exchange Commission, or SEC. These reports are also available at the SEC's website at www.sec.gov. The public may also read and copy any materials filed with the SEC at the SEC's Public Reference Room at 100 F Street, N.E., Washington D.C. 20549. Information on the operation of the Public Reference Room may be obtained by calling the SEC at 1-800-SEC-0330.

A copy of our Corporate Governance Guidelines, Code of Business Conduct and Ethics and the charters of the Audit Committee, Compensation Committee, and Nominating and Corporate Governance Committee are posted on our website, www.agios.com, under 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 $314.7 million, $198.5 million and $117.7 million for the years ended December 31, 2017, 2016 and 2015, respectively. As of December 31, 2017, we had an accumulated deficit of $798.1 million. Other than revenue from royalties on sales of IDHIFA®, we have not generated any revenue from product sales. Our most advanced product candidates are in clinical development stages and we have not yet obtained marketing approval for a product candidate, other than U.S. Food and Drug Administration's, or FDA, approval of IDHIFA® in August 2017 for the treatment of adult patients with relapsed or refractory acute myeloid leukemia, or R/R AML, and an IDH2 mutation as detected by an FDA-approved test. 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. 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: ivosidenib, AG-881, AG-348, and AG-270;
- 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;

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- add equipment and physical infrastructure to support our research and development; and
- acquire or in-license other medicines and technologies.

To become and remain profitable, we must develop and eventually commercialize a medicine or medicines with significant market potential. This will require us to be successful in a range of challenging activities, including completing preclinical testing and clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those medicines for which we may obtain marketing approval and satisfying any post-marketing requirements. We may never succeed in these activities and, even if we do, may never generate revenue that are significant or large enough to achieve profitability. 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 approvals for, our product candidates. For example, we submitted a new drug application, or NDA, for ivosidenib in IDH1 mutant-positive R/R AML in December 2017. Pursuant to the 2010 Agreement, we have certain co-promotion rights to IDHIFA® in the U.S. Although Celgene will reimburse us for our co-promotion efforts for IDHIFA® under the 2010 Agreement, if we obtain additional marketing approvals for any of our other product candidates, such as ivosidenib, 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, 2017, together with the net proceeds from our January 2018 follow-on public offering, anticipated product and royalty revenue, anticipated interest income, 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 2020. 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 additional marketing approvals and achieve product sales. 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.

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

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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 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, with the exception of IDHIFA®. We have not yet demonstrated our ability to successfully complete any large-scale or pivotal clinical trials, obtain other marketing approvals for our product candidates, 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 that may adversely affect our ability to successfully commercialize our product candidates. 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 diseases, 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. We are also focused on metabolic immuno-oncology, an emerging field of cancer research focused on altering the metabolic state of immune cells to enhance the body's immune response to cancer.

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. Any medicines that we develop may not effectively correct metabolic pathways or alter the metabolic state of immune cells. 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. In addition, even if we obtain marketing approval for one of our product candidates, we can provide no assurance that commercialization of such product candidate will be successful.

We are reliant on Celgene for the successful development and commercialization of IDHIFA®. If Celgene does not successfully commercialize IDHIFA® for the treatment of adult patients with R/R AML and an IDH2 mutation, our future prospects may be substantially harmed.

In August 2017, the FDA approved IDHIFA® for the treatment of adult patients with R/R AML and an IDH2 mutation, on the basis of an NDA submitted by Celgene. Although IDHIFA® has received FDA approval in R/R AML with an IDH2 mutation, we and Celgene are still evaluating IDHIFA® in other clinical trials. Celgene maintains worldwide development and commercial rights to IDHIFA® and Celgene will fund the development and commercialization costs related to this program, although we have certain co-commercialization and co-promotion rights to IDHIFA®. Under the 2010 Agreement, Celgene is responsible for all development costs for IDHIFA®, and we are eligible to receive up to $95.0 million in milestone payments and a tiered royalty on any net sales of products containing IDHIFA®. Thus, our ability to generate product revenue from IDHIFA® will depend heavily on Celegene's successful development and eventual commercialization of the product.

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The development and commercialization of IDHIFA® could be unsuccessful if:

- IDHIFA® becomes no longer accepted as safe, efficacious, and cost-effective for the treatment of adult patients with R/R AML and an IDH2 mutation in the medical community and by third-party payors;
- Celgene fails to continue to apply the necessary financial resources and expertise to manufacturing, marketing and selling IDHIFA®;
- Celgene does not continue to develop and implement effective marketing, sales and distribution strategies and operations for development and commercialization of IDHIFA®;
- Celgene does not continue to develop, validate and maintain a commercially viable manufacturing process for IDHIFA® that is compliant with current good manufacturing practices;
- Celgene do not successfully obtain third party reimbursement and generate commercial demand that results in sales of IDHIFA®;
- we or Celgene encounter any third party patent interference, derivation, inter partes review, post-grant review, reexamination or patent infringement claims with respect to IDHIFA®;
- Celgene does not comply with regulatory and legal requirements applicable to the sale of IDHIFA®;
- competing drug products are approved for the same indications as IDHIFA®;
- new safety risks are identified;
- IDHIFA® does not demonstrate acceptable safety and efficacy in current or future clinical trials, or otherwise does not meet applicable regulatory standards for approval in indications other than for the treatment of adult patients with R/R AML and an IDH2 mutation;
- Celgene determines to re-prioritize its commercial or development programs and reduce or terminate its efforts on the development or commercialization of IDHIFA®; or
- Celgene does not maintain or defend intellectual property rights associated with IDHIFA®.

If we or Celgene experience significant delays or an inability to successfully commercialize IDHIFA®, our business would be materially harmed.

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, which are still in clinical development. Clinical trials of our product candidates may not be successful. If we or our collaborators 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 clinical product candidates, which are ivosidenib and AG-881 for the treatment of hematological and solid tumors and AG-348 for the

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treatment of pyruvate kinase, or PK, deficiency. We have initiated clinical trials for these product candidates. In December 2017, we submitted an NDA to the FDA for ivosidenib for the treatment of patients with R/R AML and an IDH1 mutation. We also plan to submit a Marketing Authorization Application, or MAA, to the European Medicines Agency, or EMA, for ivosidenib for IDH1 mutant-positive R/R AML in the fourth quarter of 2018. In addition, we intend to initiate two global, pivotal trials of AG-348 in PK deficiency in the first half of 2018, and we also expect to initiate a phase 2 proof of concept trial of AG-348 in thalassemia in the fourth quarter of 2018. Our next most advanced cancer product candidate is AG-270. We submitted an investigational new drug application, or IND, for AG-270 in November 2017 and, in December 2017, the FDA concluded that we may proceed with a proposed phase 1 dose-escalation trial in multiple tumor types carrying a methylthioadenosine phosphorylase deletion, which we expect to initiate in the first quarter of 2018. 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 our product candidates.

The success of ivosidenib and our other 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 FDA, the EMA 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;
- the performance of any 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 any collaborators do not achieve one or more of these factors in a timely manner or at all, we or such 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 EMA, impose similar requirements. We have not previously submitted 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. In December 2017, we submitted an NDA to the FDA for ivosidenib in IDH1 mutant-positive R/R AML, and we plan to submit an MAA to the EMA for ivosidenib for IDH1 mutant-positive R/R AML in the fourth quarter of 2018. However, we can provide no assurance that we will receive regulatory approval of ivosidenib 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

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continue development or is not approvable. For instance, in December 2016, we withdrew our IND 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, also known as 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.

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;
- 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

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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.

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, Daiichi Sankyo Company, Ltd., with DS-1001b, Bayer AG, or Bayer, with BAY1436032, and Forma Therapeutics Holdings, LLC, with FT-2102, are currently conducting clinical trials in patients with IDH1 mutant positive-cancers, and Rocket Pharma LTD is in the

preclinical stages of development for a gene therapy targeting PK deficiency. As these companies and others initiate and conduct clinical trials, they may compete for eligible patients with our clinical trials of ivosidenib, AG-881 or AG-348. Competition for these patients may make it particularly difficult for us to enroll enough patients to complete our clinical trials for ivosidenib, AG-881 or AG-348 in a timely and cost-effective manner.

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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.

With the exception of IDHIFA®, 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 IND 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.

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

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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 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 some of our cancer therapeutic product candidates, including the FDA approved companion diagnostic for IDHIFA®. 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 may be unable to obtain, or may be delayed in obtaining, marketing approval for our product candidates.

In December 2017, we submitted an NDA to the FDA for ivosidenib in IDH1 mutant-positive R/R AML, and we plan to submit an MAA to the EMA for ivosidenib for IDH1 mutant-positive R/R AML in the fourth quarter of 2018. It is possible that the FDA or EMA may refuse to accept our applications for substantive review, or that the FDA or EMA may conclude after review of our data that our application is insufficient to obtain marketing approval of ivosidenib in the United States and the European Union, or E.U., respectively. If the FDA or EMA does not accept or approve our NDA for ivosidenib or the MAA for ivosidenib that we plan to submit, respectively, we may be required to conduct additional clinical trials, preclinical studies or manufacturing validation studies and submit that data to regulators before our application will be reconsidered. Depending on the extent of these or any other FDA- or EMA-required trials or studies, acceptance or approval of our NDA for ivosidenib or the MAA for ivosidenib that we plan to 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 or EMA to accept or approve our NDA for ivosidenib or the MAA for ivosidenib that we play to submit, respectively. Any delay in obtaining, or an inability to obtain, marketing approvals would prevent us from commercializing ivosidenib in the United States and/or abroad, generating revenue and achieving and sustaining profitability. If any of these outcomes occur, either to ivosidenib or to any future product candidate for which we may seek marketing approval, we may be forced to abandon our development efforts for ivosidenib or such future 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;

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- 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;
- regulatory authorities may require the addition of labeling statements, such as a “black box” warning or a contraindication, including, for example, the black box warning for differentiation syndrome on the label for IDHIFA®;
- 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.

IDHIFA®, or any of our product candidates that receive marketing approval in the future, 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 and maintain 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. Although we have established sales and marketing capabilities to support our co-promotion efforts for IDHIFA®, we are still building a sales and marketing infrastructure to sell, or participate in sales activities with our collaborators for, our other product candidates if and when they are approved.

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

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

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;

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- 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, and Abbvie Inc. (in collaboration with Roche Holdings Inc., or Roche) and Bayer are each developing or marketing 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 IDHIFA®, and other of our product candidates, if approved, will be priced at a significant premium over competitive generic products. This may make it difficult for us to achieve our business strategy of using our product candidates in combination with existing therapies or replacing existing therapies with our product candidates.

We are also pursuing product candidates to treat patients with RGDs. There are a variety of treatment options available, including a number of marketed enzyme replacement therapies, for treating patients with RGDs. In addition to currently marketed therapies, there are also a number of products that are either enzyme replacement therapies or gene therapies in various stages of clinical development to treat RGDs. These products in development may provide efficacy, safety, convenience and other benefits that are not provided by currently marketed therapies. As a result, they may provide significant competition for any of our product candidates for which we obtain 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, Bayer, Eli Lilly and Company, Roche and its subsidiary Genentech, Inc., GlaxoSmithKline plc, Merck & Co., or Merck, 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., Daiichi Sankyo

Company, Ltd. with its IDH1 mutant inhibitor DS-1001b, Forma Therapeutics Holdings LLC with its IDH1 mutant inhibitor FT-2102, Shire Plc, 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

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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.

If the FDA does not grant our products appropriate periods of data exclusivity before approving generic versions of our products, the sales of our products could be adversely affected.

With FDA approval of an NDA, the product covered by the application is specified as a “reference-listed drug” in the FDA’s publication, “Approved Drug Products with Therapeutic Equivalence Evaluations,” or the Orange Book. Manufacturers may seek approval of generic versions of reference-listed drugs through submission of abbreviated new drug applications, or ANDAs, in the United States. In support of an ANDA, a generic manufacturer need not conduct clinical trials. Rather, the applicant generally must show that its product has the same active ingredient(s), dosage form, strength, route of administration and conditions of use or labeling as the reference-listed drug and that the generic version is bioequivalent to the reference-listed drug, meaning it is absorbed in the body at the same rate and to the same extent. Generic products may be significantly less costly to bring to market than the reference-listed drug and companies that produce generic products are generally able to offer them at lower prices. Thus, following the introduction of a generic drug, a significant percentage of the sales of any reference-listed drug may be typically lost to the generic product.

The FDA may not approve an ANDA for a generic product until any applicable period of non-patent exclusivity for the reference-listed drug has expired. The Federal Food, Drug, and Cosmetic Act, or FDCA, provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity, or NCE. Specifically, in cases where such 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 that a patent covering the reference-listed drug is either invalid or will not be infringed by the generic product, in which case the applicant may submit its application four years following approval of the reference-listed drug. The FDCA also provides a period of three years of new clinical investigation, or NCI, data exclusivity in connection with the approval of a supplemental indication for the product for which a clinical trial is essential for approval.

In the event that a generic manufacturer is somehow able to obtain FDA approval without adherence to these periods of data exclusivity, the competition that our approved products may face from generic versions could negatively impact our future revenue, profitability and cash flows and substantially limit our ability to obtain a return on our investments in those product candidates.

Even if we or any 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 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

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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 as we or they commercially sell any medicines that we or they may develop. If we or our collaborators cannot successfully defend ourselves or themselves against claims that our product candidates or medicines caused injuries, we could incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

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

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Our internal computer systems, or those of any collaborators or contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

Our internal computer systems and those of any collaborators, contractors or consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. While we have not experienced any such material system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our competitive position could be harmed and the further development and commercialization of our product candidates 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, including the 2010 Agreement, the AG-881 Agreements and the 2016 Agreement. 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 with Celgene, pose the following risks to us:

- Collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations. 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 IDHIFA®, 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. For example, Celgene has elected not to participate in our planned perioperative study of ivosidenib and AG-881 in patients with low grade glioma and, pursuant to the AG-881 Agreements, we will fund the trial ourselves.
- 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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- 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 IDHIFA® 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 IDHIFA® 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 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

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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, and 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 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, 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.

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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. Although we have long-term supply agreements in place for commercial supply of ivosidenib with third-party manufacturers, we purchase the rest of our required drug supply on a purchase order basis.

We may be unable to establish any further 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
- 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 substance or drug product. 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.

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

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued 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 PTO, or become involved in opposition, derivation, revocation, reexamination, post-grant and inter partes review or interference proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize medicines without infringing third-party patent rights. Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us or otherwise provide us with any competitive advantage. Our competitors or other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner.

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

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

Competitors may infringe our patents and other intellectual property rights. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated or

interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

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

Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights and intellectual property of third parties. The biotechnology and pharmaceutical industries are characterized by extensive litigation regarding patents and

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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 PTO. 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 our 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 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

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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 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. With the exception of IDHIFA®, we and our collaborators have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction. In December 2017, we submitted an NDA to the FDA for ivosidenib in IDH1 mutant-positive R/R AML, and we plan to submit an MAA to the EMA for ivosidenib for IDH1 mutant-positive R/R AML in the fourth quarter of 2018. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. 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.

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 we submit, including our recently filed NDA for ivosidenib, 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.

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 E.U. 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. In particular, although we plan to file an MAA with EMA for ivosidenib in the future, we may not be successful in obtaining EMA approval of ivosidenib on a timely basis, or ever. Moreover, 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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Additionally, on June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the E.U., commonly referred to as Brexit. On March 29, 2017, the country formally notified the E.U. of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. Since a significant proportion of the regulatory framework in the United Kingdom is derived from E.U. directives and regulations, the referendum could materially impact the regulatory regime with respect to the approval of our product candidates in the United Kingdom or the E.U. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom and/or the E.U. and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or E.U. for our product candidates, which could significantly and materially harm our business.

A fast track designation by the FDA may not actually lead to a faster development or regulatory review or approval process, nor does it assure approval of the product candidate by FDA.

In the United States, IDHIFA® and ivosidenib received fast track designation for treatment of patients with 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 if our product candidates receive fast track designation, 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.

We, or any future collaborators, may not be able to obtain orphan drug designation or orphan drug exclusivity for our drug candidates and, even if we do, that exclusivity may not prevent the FDA or the EMA from approving competing drugs.

Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs and biologics for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a product as an orphan drug if it is a drug or biologic intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals annually in the United States.

Generally, if a product with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the EMA or the FDA from approving another marketing application for the same product for that time period. The applicable period is seven years in the United States and ten years in Europe. The European exclusivity period can be reduced to six years if a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be lost if the FDA or EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

Moreover, even after an orphan drug is approved, the FDA can subsequently approve a different product for the same condition if the FDA concludes that the later product is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care.

On August 3, 2017, the Congress passed the FDA Reauthorization Act of 2017 (FDARA). FDARA, among other things, codified the FDA’s pre-existing regulatory interpretation, to require that a drug sponsor demonstrate the clinical superiority of an orphan drug that is otherwise the same as a previously approved drug for the same rare disease in order to receive orphan drug exclusivity. The new legislation reverses prior precedent holding that the Orphan Drug Act unambiguously requires that the FDA recognize the orphan exclusivity period regardless of a showing of clinical superiority. The FDA may further reevaluate the Orphan Drug Act and its regulations and policies. We do not know if, when, or how the FDA may change the orphan drug regulations and policies in the future, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be adversely impacted.

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.

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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.

Non-compliance with E.U. 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 E.U. 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

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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; 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.

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.

Under the CURES Act and the Trump Administration's regulatory reform initiatives, the FDA's policies, regulations and guidance may be revised or revoked and that could prevent, limit or delay regulatory approval of our product candidates, which would impact our ability to generate revenue.

In December 2016, the 21st Century Cures Act, or Cures Act, was signed into law. The Cures Act, among other things, is intended to modernize the regulation of drugs and spur innovation, but its ultimate implementation is unclear. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would adversely affect our business, prospects, financial condition and results of operations.

We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. For example, certain policies of the Trump administration may impact our business and industry. Namely, the Trump administration has taken several executive actions, including the issuance of a number of Executive Orders, that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. An under-staffed FDA could result in delays in the FDA's responsiveness or in its ability to review submissions or applications, issue regulations or guidance, or implement or enforce regulatory requirements in a timely fashion or at all. Moreover, on January 30, 2017, President Trump issued an Executive Order, applicable to all executive agencies, including the FDA, which requires that for each notice of proposed rulemaking or final regulation to be issued in fiscal year 2017, the agency shall identify at least two existing regulations to be repealed, unless prohibited by law.

These requirements are referred to as the “two-for-one” provisions. This Executive Order includes a budget neutrality provision that requires the total incremental cost of all new regulations in the 2017 fiscal year, including repealed regulations, to be no greater than zero, except in limited circumstances. For fiscal years 2018 and beyond, the Executive Order requires agencies to identify regulations to offset any incremental cost of a new regulation and approximate the total costs or savings associated with each new regulation or repealed regulation. In interim guidance issued by the Office of Information and Regulatory Affairs within OMB on February 2, 2017, the administration indicates that the “two-for-one” provisions may apply not only to agency regulations, but also to significant agency guidance documents. In addition, on February 24, 2017, President Trump issued an executive order directing each affected agency to designate an agency official as a “Regulatory Reform Officer” and establish a “Regulatory Reform Task Force” to implement the two-for-one provisions

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and other previously issued executive orders relating to the review of federal regulations, however it is difficult to predict how these requirements will be implemented, and the extent to which they will impact the FDA's ability to exercise its regulatory authority. If these executive actions impose constraints on the FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted.

Current and future legislation may increase the difficulty and cost for us and any future collaborators to obtain marketing approval and commercialize our drug 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 drug candidates, restrict or regulate post-approval activities and affect our ability, or the ability of any future collaborators, to profitably sell any drugs 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 in additional downward pressure on the price that we, or any future collaborators, may receive for any approved drugs.

Among the provisions of the Patient Protection and Affordable Care Act, or ACA, of potential importance to our business and our drug 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;
- 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 to eligible beneficiaries during their coverage gap period, as a condition for a manufacturer's outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability;
- 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; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

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 will stay in effect through 2024 unless additional Congressional action is taken, and the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several types of 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 otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Further, there have been several recent U.S. congressional inquiries and proposed state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products.

We expect that these healthcare reforms, 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 and/or the level of reimbursement physicians receive for administering any approved product we might bring to market. Reductions in reimbursement levels may negatively impact the prices we receive or the frequency with which our products are prescribed or administered. Any reduction in reimbursement from Medicare or other government

programs may result in a similar reduction in payments from private payors. Since enactment of the ACA, there have been numerous legal challenges and Congressional actions to repeal and replace provisions of the law. In May 2017, the U.S. House of Representatives passed legislation known as the American Health Care Act of 2017. Thereafter, the Senate Republicans introduced and then updated a bill to replace the

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ACA known as the Better Care Reconciliation Act of 2017. The Senate Republicans also introduced legislation to repeal the ACA without companion legislation to replace it, and a "skinny" version of the Better Care Reconciliation Act of 2017. In addition, the Senate considered proposed healthcare reform legislation known as the Graham-Cassidy bill. None of these measures was passed by the U.S. Senate.

The Trump Administration has also taken executive actions to undermine or delay implementation of the ACA. In January 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. In October 2017, the President signed a second Executive Order allowing for the use of association health plans and short-term health insurance, which may provide fewer health benefits than the plans sold through the ACA exchanges. At the same time, the Administration announced that it will discontinue the payment of cost-sharing reduction (CSR) payments to insurance companies until Congress approves the appropriation of funds for such CSR payments. The loss of the CSR payments is expected to increase premiums on certain policies issued by qualified health plans under the ACA. A bipartisan bill to appropriate funds for CSR payments was introduced in the Senate, but the future of that bill is uncertain.

More recently, with enactment of the Tax Cuts and Jobs Act of 2017, which was signed by the President on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, will become effective in 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. Further, each chamber of the Congress has put forth multiple bills designed to repeal or repeal and replace portions of the ACA. Although none of these measures has been enacted by Congress to date, Congress may consider other legislation to repeal and replace elements of the ACA. The Congress will likely consider other legislation to replace elements of the ACA, during the next Congressional session.

We will continue to evaluate the effect that the ACA and its possible repeal and replacement could have on our business. It is possible that repeal and replacement initiatives, if enacted into law, could ultimately result in fewer individuals having health insurance coverage or in individuals having insurance coverage with less generous benefits. While the timing and scope of any potential future legislation to repeal and replace ACA provisions is highly uncertain in many respects, it is also possible that some of the ACA provisions that generally are not favorable for the research-based pharmaceutical industry could also be repealed along with ACA coverage expansion provisions. Accordingly, such reforms, if enacted, 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 or commercialize product candidates.

The costs of prescription pharmaceuticals in the United States has also been the subject of considerable discussion in the United States, and members of Congress and the Administration have stated that they will address such costs through new legislative and administrative measures. The pricing of prescription pharmaceuticals is also subject to governmental control outside the United States. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost effectiveness of our product candidates to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our ability to generate revenues and become profitable could be impaired.

Moreover, legislative and regulatory proposals have also been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical drugs. 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 drug candidates, if any, may be. In addition, increased scrutiny by the United States 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 drug labeling and post-marketing testing and other requirements.

We are subject to U.S. and foreign anti-corruption and anti-money laundering laws with respect to our operations and non-compliance with such laws can subject us to criminal and/or civil liability and harm our business.

We are subject to the U.S. Foreign Corrupt Practices Act of 1977, as amended, or the FCPA, the U.S. domestic bribery statute contained in 18 U.S.C. § 201, the U.S. Travel Act, the USA PATRIOT Act, and possibly other state and national anti-bribery and anti-money laundering laws in countries in which we conduct activities. Anti-corruption laws are interpreted broadly and prohibit companies and their employees, agents, third-party intermediaries, joint venture partners and collaborators from authorizing, promising, offering, or providing, directly or indirectly, improper payments or benefits to recipients in the public or private sector. We may have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. In addition, we may engage third party intermediaries to promote our clinical research activities abroad and/or to obtain necessary permits, licenses, and other regulatory approvals. We can be held

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liable for the corrupt or other illegal activities of these third-party intermediaries, our employees, representatives, contractors, partners, and agents, even if we do not explicitly authorize or have actual knowledge of such activities. Noncompliance with anti-corruption and anti-money laundering laws could subject us to whistleblower complaints, investigations, sanctions, settlements, prosecution, other enforcement actions, disgorgement of profits, significant fines, damages, other civil and criminal penalties or injunctions, suspension and/or debarment from contracting with certain persons, the loss of export privileges, reputational harm, adverse media coverage, and other collateral consequences. If any subpoenas, investigations, or other enforcement actions are launched, or governmental or other sanctions are imposed, or if we do not prevail in any possible civil or criminal litigation, our business, results of operations and financial condition could be materially harmed. In addition, responding to any action will likely result in a materially significant diversion of management's attention and resources and significant defense and compliance costs and other professional fees. In certain cases, enforcement authorities may even cause us to appoint an independent compliance monitor which can result in added costs and administrative burdens.

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.

If we obtain approval to commercialize our product candidates outside of the United States, a variety of risks associated with international operations could materially adversely affect our business.

We expect that we will be subject to additional risks in commercializing our product candidates outside the United States, including:

- different regulatory requirements for approval of drugs in foreign countries;
- reduced protection for intellectual property rights;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geopolitical actions, including war and terrorism or natural disasters including earthquakes, typhoons, floods and fires.

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

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for any of our executives or other employees. The loss of the services of any of these persons could impede the achievement of our research, development and commercialization objectives.

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

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

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA regulations, provide accurate information to the FDA, comply with manufacturing standards we have established, comply with federal and state 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 and Other Matters

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

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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. 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;

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- 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, including fluctuations in levels of royalties on sales of IDHIFA®, or results 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.

If any of the forgoing matters were to occur, or if our operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. In the past, following periods of volatility in the market price of a company's securities, securities class-action litigation often has been instituted against that company. Such litigation, if instituted against us, could cause us to incur substantial costs to defend such claims and divert management's attention and resources, which could seriously harm our business, financial condition, results of operations and prospects.

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.

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, 2017, 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

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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, or the IRC, 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. We completed a review of our changes in ownership through December 31, 2017, and determined that we had a qualified ownership change since our last review as of December 31, 2011. We do not expect that this or any previous changes of ownership will result in our net operating loss carryforwards or certain other tax attributes expiring unutilized. Future ownership changes under Section 382 may limit the amount of net operating loss and tax credit carryforwards that we could potentially utilize to reduce future tax liabilities.

The recently passed comprehensive tax reform bill could adversely affect our business and financial condition.

On December 22, 2017, President Trump signed into law new legislation that significantly revised the Internal Revenue Code of 1986, as amended. The newly enacted federal income tax law, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limitation of the tax deduction for interest expense to 30% of adjusted earnings (except for certain small businesses), limitation of the deduction for net operating losses to 80% of current year taxable income and elimination of net operating loss carrybacks, one time taxation of offshore earnings at reduced rates regardless of whether they are repatriated, elimination of U.S. tax on foreign earnings (subject to certain important exceptions), immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifying or repealing many business deductions and credits. Notwithstanding the reduction in the corporate income tax rate, the overall impact of the new federal tax law is uncertain and our business and financial condition could be adversely affected. In addition, it is uncertain how various states will respond to the newly enacted federal tax law. The impact of this tax reform on holders of our common stock is also uncertain and could be adverse. We urge our stockholders to consult with their legal and tax advisors with respect to this legislation and the potential tax consequences of investing in or holding our common stock.

Our effective tax rate may fluctuate, and we may incur obligations in tax jurisdictions in excess of accrued amounts.

We are subject to taxation in numerous U.S. states and territories. As a result, our effective tax rate is derived from a combination of applicable tax rates in the various places that we operate. In preparing our financial statements, we estimate the amount of tax that will become payable in each of such places. Nevertheless, our effective tax rate may be different than experienced in the past due to numerous factors, including passage of the newly enacted federal income tax law, changes in the mix of our profitability from state to state, the results of examinations and audits of our tax filings, our inability to secure or sustain acceptable agreements with tax authorities, changes in accounting for income taxes and changes in tax laws. Any of these factors could cause us to experience an effective tax rate significantly different from previous periods or our current expectations and may result in tax obligations in excess of amounts accrued in our financial statements.

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 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.

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

We currently lease approximately 146,030 square feet at 88 Sidney Street, Cambridge, Massachusetts. This lease, as amended, expires on January 31, 2025. We also lease approximately 27,100 square feet at 64 Sidney Street, Cambridge, Massachusetts. This lease also expires on January 31, 2025. At the end of the initial lease period, we have the option to extend the leases at one or both facilities for two consecutive five year periods 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

As of December 31, 2017, we were not a party to any material legal or arbitration proceedings. No governmental proceedings are pending or, to our knowledge, contemplated against us. We are not a party to any material proceedings in which any director, member of senior management or affiliate of ours is either a party adverse to us or our subsidiaries or has a material interest adverse to us or our subsidiaries.

Item 4. Mine Safety Disclosures

Not applicable.

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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, 2017 and 2016.

2017	High	Low
First Quarter	$58.65	$39.24
Second Quarter	$59.58	$45.11
Third Quarter	$67.72	$50.91
Fourth Quarter	$72.73	$51.62
2016	High	Low
First Quarter	$66.87	$33.50
Second Quarter	$66.74	$39.36
Third Quarter	$54.99	$35.84
Fourth Quarter	$67.74	$40.59

Holders

As of February 9, 2018, 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, Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters, 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 Securities and Exchange Commission, or 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 the NASDAQ Biotechnology Index from July 24, 2013 (the first date that shares of our common stock were publicly traded) through December 31, 2017. The comparison assumes $100 was invested after the market closed on July 24, 2013 in our common stock and in each of the foregoing indices, and it assumes reinvestment of dividends, if any. The stock price performance included in this graph is not necessarily indicative of future stock price performance.

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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 2017.

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Item 6. Selected Consolidated Financial Data

You should read the following selected historical consolidated financial data along with Item 7, Management's Discussion and Analysis of Financial Condition and Results of Operations, and the consolidated financial statements and related notes thereto contained 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.

The financial information included in the tables below are derived from audited financial statements.

Our consolidated statements of operations are summarized as follows (in thousands, except per share amounts):

	Years Ended December 31,				
	2017	2016	2015	2014	2013
Consolidated Statements of Operations:					
Collaboration revenue – related party	$41,074	$69,892	$59,119	$65,358	$25,548
Royalty revenue – related party	1,937	—	—	—	—
Total revenue	43,011	69,892	59,119	65,358	25,548
Operating expenses:					
Research and development (net of $7,811, $19,714 and $25,173 of cost reimbursement from related party for the years ended December 31, 2017, 2016 and 2015, respectively)	292,681	220,163	141,827	100,371	54,502
General and administrative	71,124	50,714	35,992	19,120	9,929
Total operating expenses	363,805	270,877	177,819	119,491	64,431
Loss from operations	(320,794)	(200,985)	(118,700)	(54,133)	(38,883)
Interest income	6,124	2,514	968	203	55
Loss before (benefit) provision for income taxes	(314,670)	(198,471)	(117,732)	(53,930)	(38,828)
(Benefit) provision for income taxes	—	—	—	(426)	579
Net loss	(314,670)	(198,471)	(117,732)	(53,504)	(39,407)
Cumulative preferred stock dividends	—	—	—	—	(4,162)
Net loss applicable to common stockholders	$(314,670)	$(198,471)	$(117,732)	$(53,504)	$(43,569)
Net loss per share – basic and diluted	$(6.75)	$(5.07)	$(3.15)	$(1.59)	$(2.83)
Weighted-average number of common shares used in computing net loss per share – basic and diluted	46,587,631	39,126,400	37,429,262	33,667,024	15,415,373

Our consolidated balance sheets are summarized as follows (in thousands):

	December 31,				
	2017	2016	2015	2014	2013
Consolidated Balance Sheet:					
Cash, cash equivalents and marketable securities	$567,750	$573,564	$375,907	$467,447	$193,894
Total assets	614,397	619,094	420,065	491,904	201,205
Total liabilities	238,894	260,503	74,947	67,538	69,723
Common stock	49	42	38	37	31
Additional paid-in capital	1,174,904	842,013	630,078	591,334	244,881
Accumulated deficit	(798,061)	(483,151)	(284,680)	(166,948)	(113,444)
Total stockholders' equity	375,503	358,591	345,118	424,366	131,482

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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 "Item 1A, Risk Factors" 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 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 diseases, or RGDs, which are diseases that are directly caused by changes in genes or chromosomes, often passed from one generation to the next. Most RGDs are often associated with severe or life-threatening features. The incidence of a single RGD can vary widely but is generally very infrequent, usually equal to or less than one per 100,000 births. In both areas of cancer and RGDs, we are seeking to unlock the biology of cellular metabolism as a platform to create transformative therapies.

Our first commercial cancer product is IDHIFA®. In August 2017, the U.S. Food and Drug Administration, or FDA, granted our collaboration partner Celgene Corporation, or Celgene, approval of IDHIFA® for the treatment of adult patients with relapsed or refractory acute myeloid leukemia, or R/R AML, and an isocitrate dehydrogenase 2, or IDH2, mutation as detected by an FDA-approved test. IDHIFA®, an oral targeted inhibitor of the mutated IDH2 enzyme, is the first and only FDA-approved therapy for patients with R/R AML and an IDH2 mutation.

Our most advanced clinical cancer product candidates are ivosidenib, which targets mutated isocitrate dehydrogenase 1, or IDH1, and AG-881, which is a brain-penetrant pan-IDH mutant inhibitor. These mutations are found in a wide range of hematological malignancies and solid tumors. In December 2017, we submitted a new drug application, or NDA, to the FDA for ivosidenib for the treatment of patients with R/R AML and an IDH1 mutation. We plan to submit an Marketing Authorization Application, or MAA, to the European Medicines Agency, or EMA, for ivosidenib for IDH1 mutant-positive R/R AML in the fourth quarter of 2018.

Our next most advanced cancer product candidate is AG-270, an inhibitor of methionine adenosyltransferase 2a, or MAT2A. We submitted an investigational new drug application, or IND, for AG-270 in November 2017, and in December 2017 the FDA concluded that we may proceed with our planned phase 1 dose-escalation trial of AG-270 in multiple tumor types carrying a methylthioadenosine phosphorylase, or MTAP, deletion.

Our most advanced preclinical cancer product candidate is an inhibitor of the metabolic enzyme dihydroorotate dehydrogenase, or DHODH. We plan to submit an IND for our DHODH inhibitor for the treatment of hematologic malignancies in the fourth quarter of 2018.

The lead product candidate in our RGD program, AG-348, targets pyruvate kinase-R for the treatment of pyruvate kinase, or PK, deficiency. PK deficiency is a rare genetic disorder that often results in severe hemolytic anemia, jaundice and lifelong conditions associated with chronic anemia and secondary complications due to inherited mutations in the pyruvate kinase enzyme within red blood cells, or RBCs. We intend to initiate two global, pivotal trials of AG-348 in PK deficiency in the first half of 2018: ACTIVATE-T, a single arm trial of approximately 20 regularly transfused patients, is expected to initiate in the first quarter of 2018, and ACTIVATE, a 1:1 randomized, placebo-controlled trial of approximately 80 patients who do not receive regular transfusions, is expected to initiate in the second quarter of 2018. We also expect to initiate a phase 2 proof of concept trial of AG-348 in thalassemia in the fourth quarter of 2018.

In addition to the aforementioned development programs, we are seeking to advance a number of early-stage discovery programs in the areas of cancer metabolism, RGDs and metabolic immuno-oncology, or 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.

Celgene Collaboration Agreements

2016 Agreement

In May 2016, we entered into the 2016 Agreement with Celgene, which is focused on MIO, or the 2016 Agreement. In addition to new programs identified under the 2016 Agreement, both parties also agreed that all future development and commercialization of two remaining cancer metabolism programs discovered under the 2010 Agreement, including AG-270, our MAT2A inhibitor, will be governed by the 2016 Agreement.

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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, and 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 preclinical and clinical development for such program through the 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. We may conduct further research and preclinical and clinical development activities on any continuation program, at our expense, through the completion of an initial phase 1 dose escalation study.

We granted Celgene the right to obtain exclusive options for 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: (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 two 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.

Ivosidenib Letter Agreement

On May 17, 2016, we entered into a letter agreement with Celgene regarding ivosidenib, or the Ivosidenib Letter Agreement. Under the Ivosidenib Letter Agreement, 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 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 Ivosidenib Letter Agreement, we obtained global rights to ivosidenib and the IDH1 program. Neither party will have any further financial obligation, including royalties or milestone payments, to the other concerning ivosidenib or the IDH1 program. Under the terms of the Ivosidenib Letter Agreement, the parties also agreed to conduct specified transitional activities in connection with the termination. In addition, pursuant to the Ivosidenib Letter Agreement, the parties are released from their exclusivity obligations under the 2010 Agreement with respect to the IDH1 program. The Ivosidenib 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, we entered into a joint worldwide development and profit share collaboration and license agreement with Celgene, and our wholly owned subsidiary, Agios International Sarl, 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 joint worldwide collaboration focused on the development and commercialization of AG-881 products. Under the terms of the AG-881 Agreements, we received an initial upfront

payment of $10.0 million in May 2015 and are eligible to receive milestone-based payments. The parties will split all worldwide development costs equally, subject to specified exceptions, as well as any profits from any net sales of, or commercialization losses related to, licensed AG-881 products. Either party may, at its own expense and with the other party's permission, undertake additional development activities outside of the scope of the development plan agreed upon with the other party.

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2010 Agreement

In April 2010, we entered into a collaboration agreement with Celgene focused on cancer metabolism, or 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 our 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 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 is the lead development candidate, the sole program remaining under the 2010 Agreement is IDHIFA®, a co-commercialized licensed program for which Celgene leads and funds global development and commercialization activities. We have exercised our right to participate in a portion of commercialization activities in the United States for IDHIFA® in accordance with the applicable commercialization plan.

Financial Operations Overview

General

Since inception, our operations have primarily 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.

Additionally, since inception, we have incurred significant operating losses. Our net losses were $314.7 million, $198.5 million and $117.7 million for the years ended December 31, 2017, 2016 and 2015, respectively. As of December 31, 2017, we had an accumulated deficit of $798.1 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: IDHIFA®, ivosidenib, AG-881, AG-348, and AG-270; 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.

Revenue

Through December 31, 2017, we have not generated any revenue from product sales. All of our revenue to date has been derived from our collaborations or royalty revenue on sales of IDHIFA®. In the future, we will seek to generate revenue from a combination of product sales, royalties on product sales, cost reimbursements, milestone payments, and upfront payments to the extent we enter into future collaborations or licensing agreements.

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 IDHIFA®, ivosidenib, AG-881, AG-348, AG-270, 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 NDA enabling toxicology and clinical 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

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- maintaining an acceptable safety profile of the products following approval.

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

Research and development 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 the maintenance of facilities, insurance and other operating costs.

The following summarizes our most advanced programs:

IDHIFA®

IDHIFA® 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 August 2017, the FDA granted Celgene approval of IDHIFA® for the treatment of adult patients with R/R AML and an IDH2 mutation as detected by an FDA-approved test.

The FDA has granted orphan drug designation for IDHIFA® for treatment of patients with AML and fast track designation for treatment of patients with AML that harbor an IDH2 mutation, and the EMA granted orphan drug designation for IDHIFA® for the treatment of AML.

We continue to evaluate IDHIFA® in the following clinical trials, which are led and funded by Celgene:

- A phase 1/2 multicenter, open-label, clinical trial, initially conducted by us but which Celgene has assumed primary responsibility for, to assess the safety, clinical activity, and tolerability of IDHIFA® in patients with advanced hematologic malignancies with an IDH2 mutation.
- A phase 1b, multicenter, international, open-label clinical trial, conducted by us, to evaluate the safety and clinical activity of IDHIFA® or ivosidenib 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.
- A phase 1/2 frontline combination clinical trial, conducted by Celgene, of either IDHIFA® or ivosidenib 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 the IDHIFA® investigational combination versus single-agent VIDAZA® using a primary endpoint of overall response rate, or ORR.
- IDHENTIFY, an international phase 3, multi-center, open-label, randomized clinical trial, conducted by Celgene, designed to compare the efficacy and safety of IDHIFA® 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.

We plan to support, with Celgene, the initiation of an intergroup sponsored, global, registration-enabling phase 3 trial combining ivosidenib or IDHIFA® and standard induction (7+3) and consolidation chemotherapy with a primary endpoint of event-free survival in frontline AML patients with an IDH1 or IDH2 mutation in the fourth quarter of 2018.

Ivosidenib

Ivosidenib is our wholly owned, 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. The FDA has granted us fast track designation to ivosidenib for treatment of patients with AML that harbor an IDH1 mutation and orphan drug designation for ivosidenib for treatment of patients with AML. The FDA has also granted fast-track designation to ivosidenib for treatment of patients with previously treated, unresectable or metastatic cholangiocarcinoma with and IDH1 mutation. In December 2017, we submitted

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an NDA to the FDA for ivosidenib for the treatment of patients with R/R AML and an IDH1 mutation. We plan to submit an MAA to the EMA for ivosidenib for IDH1 mutant-positive R/R AML in the fourth quarter of 2018.

We are evaluating ivosidenib in the following clinical trials:

- 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.
- As discussed above, a phase 1b, multicenter, international, open-label clinical trial to evaluate the safety and clinical activity of IDHIFA® or ivosidenib 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.
- As discussed above, a phase 1/2 frontline combination clinical trial, conducted by Celgene, of either IDHIFA® or ivosidenib in combination with VIDAZA® (azacitidine) in newly diagnosed AML patients not eligible for intensive chemotherapy.
- AGILE, a global, registration-enabling phase 3 clinical trial, combining ivosidenib and VIDAZA® in newly diagnosed AML patients with an IDH1 mutation who are ineligible for intensive chemotherapy.
- 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, cholangiocarcinoma, and chondrosarcoma.
- ClarIDHy, a registration-enabling phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial of ivosidenib in previously-treated patients with nonresectable or metastatic cholangiocarcinoma with an IDH1 mutation.

As discussed above, we plan to support, with Celgene, the initiation of an intergroup sponsored, global, registration-enabling phase 3 trial combining ivosidenib or IDHIFA® and standard induction (7+3) and consolidation chemotherapy with a primary endpoint of event-free survival in frontline AML patients with an IDH1 or IDH2 mutation in the fourth quarter of 2018.

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 are currently focusing our development efforts for AG-881 in glioma.

We are evaluating AG-881 in 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.

In the first half of 2018, we intend to initiate a perioperative study with ivosidenib and AG-881 in low grade glioma to further investigate their effects on brain tumor tissue. Pursuant to the AG-881 Agreements, Celgene has elected not to participate in this clinical trial and, as a result, we will fund the trial ourselves. Celgene will continue to co-fund the ongoing phase 1 trials of AG-881 described above.

AG-348: PK Deficiency Program

AG-348 is an orally available small molecule and a potent activator of the wild-type (normal) and mutated PKR enzyme, one of several tissue-specific isoforms of the PK enzyme. We have shown that AG-348 can restore Adenosine-5’-triphosphate levels and decrease 2,3-diphosphoglycerate, or 2,3-DPG, levels in blood sampled from patients with PK deficiency when 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, and provides for potential expansion opportunities into other anemias. The FDA granted us orphan drug designation for AG-348 for treatment of patients with 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. The multi-center, randomized trial includes two arms with up to 25 patients each.

We intend to initiate two global, pivotal trials of AG-348 in PK deficiency in the first half of 2018: ACTIVATE-T, a single arm trial of approximately 20 regularly transfused patients, is expected to initiate in the first quarter of 2018, and ACTIVATE, a 1:1 randomized, placebo-controlled trial of 80 patients who do not receive regular transfusions, is

expected to initiate in the second quarter of 2018.

In addition to the above planned and ongoing clinical trials of AG-348, we plan to initiate a phase 2 proof of concept trial of AG-348 in thalassemia in the fourth quarter of 2018.

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AG-270: Targeting MAT2A for the treatment of MTAP-deleted cancers

AG-270, a MAT2A inhibitor, is our development candidate focused on MTAP-deleted cancers. We submitted an IND for AG-270 in November 2017 and, in December 2017, the FDA concluded that we may proceed with a proposed phase 1 dose-escalation trial in multiple tumor types carrying an MTAP deletion, which we expect to initiate in the first quarter of 2018.

Targeting DHODH for the treatment of hematologic malignancies

In January 2018, we announced that we plan to submit an IND in the fourth quarter of 2018 for our latest development candidate, an inhibitor of DHODH, licensed by us from Aurigene Discovery Technologies Limited, for the treatment of hematologic malignancies. We have discovered a lineage-specific dependence on DHODH in hematologic malignancies, particularly AML and diffuse large B-cell lymphoma. DHODH catalyzes a critical step in the biosynthesis of pyridimidines, which are critical for the production of RNA and DNA. We believe that DHODH inhibition will be differentiated from standard-of-care therapies, both by exhibiting activity in cancers that are resistant to standard-of-care chemotherapeutics and through a mechanism of anti-tumor effect that combines cell growth arrest and cellular differentiation.

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, commercial, 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.

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 the Financial Accounting Standards Board's, or FASB, Accounting Standards Codification, or 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;

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- the seller's price to the buyer is fixed or determinable; and
- collectability is reasonably assured.

Amounts received prior to satisfying the revenue recognition criteria are recorded as deferred revenue. Amounts expected to be recognized as revenue within the 12 months following the balance sheet date are classified current and amounts not expected to be recognized as revenue within the 12 months following the balance sheet date are classified as non-current.

Collaboration and License Revenue

We account for the collaboration agreements with Celgene under ASC 605-25, Revenue Recognition - Multiple-Element Arrangements, or 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.

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 our best estimate of selling price, or BESP, 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.

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 our performance obligations under the unit of accounting. Determining the total estimated level of effort required to complete all performance obligations requires 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 with Celgene are recognized as revenue, provided that we are acting as the 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 apply the provisions of ASC 605-28, Revenue Recognition – Milestone Method, or ASC 605-28, pursuant to which 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. 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) our 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 our 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.

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. Certain service providers invoice us 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

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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 stock-based compensation awards in accordance with ASC 718, Compensation –Stock Compensation, or ASC 718. For stock-based awards granted to employees and to members of the board of directors for their services 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 us 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.

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 approach, the weighted-average expected life is presumed to be the average of the contractual term of ten years and the weighted-average vesting term of the our stock options, taking into consideration multiple vesting tranches. We utilize this method due to lack of historical data and the plain-vanilla nature of our share-based awards.

Volatility. We use a weighted-average of expected volatility based on the volatilities of a representative group of publicly traded biopharmaceutical companies, including ourselves. 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.

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. We account for forfeitures as they occur and, therefore, do not estimate forfeitures.

For awards subject to service-based vesting conditions, we recognize stock-based compensation expense 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 over the remaining service period if the performance condition is considered probable of achievement using management’s best estimates.

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Results of Operations

Comparison of years ended December 31, 2017 and 2016

The following table summarizes our results of operations for the years ended December 31, 2017 and 2016, together with the changes in those items in dollars and as a percentage ($ in thousands):

	Years Ended December 31,			
	2017	2016	$ Change	% Change
Collaboration revenue – related party	$41,074	$69,892	$(28,818)	