AGIOS PHARMACEUTICALS INC
Form 10-K
February 14, 2019
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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, 2018

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 every Interactive Data File required to be submitted 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 such files). Yes No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) 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 the 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	Smaller reporting company	Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended 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 29, 2018 (based on the last reported sale price on the Nasdaq Global Select Market as of such date) was $4,271,074,700.

As of February 8, 2019, there were 58,395,419 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 2019 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, 2018 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 1 and 2, or IDH1 and IDH2, respectively, mutations, pyruvate kinase-R, methionine adenosyltransferase 2a, or MAT2A, and dihydroorotate dehydrogenase, or DHODH, as therapeutic targets;

•the potential benefits of our product and product candidates targeting IDH1 or IDH2 mutations, pyruvate kinase-R, MAT2A or DHODH, including TIBSOVO® (ivosidenib), IDHIFA® (enasidenib), vorasidenib (AG-881), mitapivat, AG-270 and AG-636;

•our plans to develop and commercialize our product candidates, including our ability to successfully commercialize TIBSOVO® and to successfully commercialize IDHIFA® with our partner Celgene Corporation, or Celgene;

•our collaborations with Celgene and CStone Pharmaceuticals, or CStone;

•our ability to establish and maintain additional collaborations or obtain additional funding;

•the timing or likelihood of regulatory filings and approvals, including the Marketing Authorization Application, or MAA, that we submitted in December 2018 to the European Medicines Agency, or EMA, for TIBSOVO® for the treatment of adult patients with relapsed or refractory acute myeloid leukemia, or R/R AML, with an IDH1 mutation; the supplemental new drug application, or sNDA, that we submitted in December 2018 to the U.S. Food and Drug Administration, or FDA, for TIBSOVO® for the treatment of patients with newly diagnosed AML with an IDH1 mutation who are not eligible for standard treatment; and the sNDA for TIBSOVO® for second line or later IDH1 mutant-positive cholangiocarcinoma that we plan to submit to the FDA by the end of 2019;

•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.

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You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

Item 1. Business

We are a biopharmaceutical company committed to the fundamental transformation of patients' lives through scientific leadership in the field of cellular metabolism and adjacent areas of biology, with the goal of making transformative, first- or best-in-class medicines for the treatment of cancer and rare genetic diseases, or RGDs. To address both cancer and RGDs, we take a systems biology approach to deeply understand disease states, drive the discovery and validation of novel therapeutic targets, and define patient selection strategies, thereby increasing the probability that our experimental medicines will have the desired therapeutic effect.

In July 2018, the FDA granted us approval of our wholly-owned product, TIBSOVO® (ivosidenib) for the treatment of adult patients with R/R AML with a susceptible IDH1 mutation as detected by an FDA-approved test. TIBSOVO®, an oral targeted inhibitor of the mutated IDH1 enzyme, is the first and only FDA-approved therapy for patients with R/R AML and an IDH1 mutation. In December 2018, we submitted an MAA to the EMA for TIBSOVO® for the treatment of adult patients with R/R AML. Also in December 2018, we submitted a sNDA to the FDA for TIBSOVO® for the treatment of patients with newly diagnosed AML with an IDH1 mutation who are not eligible for standard treatment. In addition, we are currently evaluating ivosidenib in the clinical trials described below.

Our other commercial cancer product is IDHIFA® (enasidenib). In August 2017, the FDA granted our collaboration partner 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. We are eligible to receive royalties at tiered low-double digit to mid-teen percentage rates on any net sales of IDHIFA® and have exercised our rights to provide up to one-third of the field-based commercialization efforts in the United States. Celgene has submitted an MAA to the EMA for IDHIFA® for IDH2 mutant-positive AML. In addition, we and Celgene are currently evaluating enasidenib in the clinical trials described below.

Our pre-commercial clinical cancer product candidates are vorasidenib (AG-881), AG-270, and AG-636.

Vorasidenib (AG-881) is a brain-penetrant pan-IDH mutant inhibitor. These mutations are found in a wide range of hematological malignancies and solid tumors. We are currently evaluating vorasidenib (AG-881) in the clinical trials described below. We expect to initiate a registration-enabling phase 3 study of vorasidenib (AG-881) in low-grade glioma with an IDH1 mutation by the end of 2019.

AG-270 is an orally available selective potent inhibitor of MAT2A. We are currently evaluating AG-270 in a phase 1 dose-escalation trial in multiple tumor types carrying a methylthioadenosine phosphorylase, or MTAP, deletion, and expect to complete dose escalation and initiate dose expansion arms of this trial in the first half of 2019.

AG-636 is an inhibitor of the metabolic enzyme DHODH. In October 2018, we submitted an investigational new drug application, or IND, for AG-636 for the treatment of hematologic malignancies, which was accepted by the FDA in November 2018. We expect to initiate a phase 1 dose-escalation trial of AG-636 in lymphoma in the first half of 2019.

The lead product candidate in our RGD portfolio, mitapivat, 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. In April 2018, we initiated ACTIVATE-T, a single arm, global, pivotal trial of mitapivat in approximately 20 regularly transfused patients with PK deficiency. In June 2018, we initiated ACTIVATE, a 1:1 randomized, placebo-controlled, global, pivotal trial of mitapivat in approximately 80 patients with PK deficiency who do not receive regular transfusions. We also initiated a phase 2 proof of concept trial of mitapivat in thalassemia in December 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.

Whenever possible, we focus our clinical development strategy on a targeted 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

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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 can 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 sustainable, multi-product company, based on our expertise in cellular metabolism and adjacent biology 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 discovery and development of novel medicines to transform the lives of patients with cancer and RGDs.

•Maintaining our competitive advantage and focus in the field of cellular metabolism 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.

•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 are driven by 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

severe side effects,

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

Cytotoxic chemotherapies

The earliest approach to cancer treatment was to develop drugs, referred to as cytotoxic drugs, 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 checkpoint inhibitors (e.g., Keytruda®, Opdivo® and Yervoy®) which block the inactivation of endogenous T cells and allow them to attack the tumor; 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 and utilization of nutrients into the cell by 200-400 fold compared to normal cells. 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

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efforts in the MIO field are governed by our 2016 global research and collaboration agreement with Celgene, described in more detail below.

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 EU. 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 products and most advanced product candidates as of February 1, 2019, 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

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metabolism. The Krebs cycle converts an essential cellular metabolite called isocitrate into another metabolite, alpha-ketoglutarate (a-ketoglutarate), both of which are critically important for cellular function and the creation of energy. In humans, there are three forms of the IDH enzyme, IDH1, IDH2, and IDH3, but only IDH1 and IDH2 appear to be mutated in cancers. IDH1 and IDH2 catalyze the 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 can 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 ivosidenib and enasidenib, our lead inhibitors of mutant IDH1 and IDH2, 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 IDH1 and IDH2 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	~10-14%
	Low grade glioma	~80%
IDH2	AML	~9-13%

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

Ivosidenib

Ivosidenib is an orally available, selective, potent inhibitor of the mutated IDH1 protein, making it a highly targeted therapeutic candidate for the treatment of patients with cancers that harbor IDH1 mutations. We hold worldwide development and commercial rights to ivosidenib and have licensed certain development and commercialization rights to ivosidenib in mainland China, Hong Kong, Macau, and Taiwan to CStone, pursuant to an exclusive license agreement with CStone, or the CStone Agreement, discussed more fully below. We will fund the future development and commercialization costs related to this program with the exception of development and commercialization activities of CStone under the CStone Agreement. 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.

In July 2018, the FDA approved TIBSOVO® for the treatment of adult patients with R/R AML and a susceptible IDH1 mutation. The FDA's approval of TIBSOVO® in R/R AML was based on clinical data from a phase 1 open-label, single-arm, multicenter dose-escalation and expansion trial of adult patients with advanced R/R AML and an IDH1 mutation. In December 2018, we submitted an MAA to the EMA for TIBSOVO® for the treatment of adult patients with R/R AML. Also in December 2018, we submitted a sNDA to the FDA for TIBSOVO® for the treatment of patients with newly diagnosed AML with an IDH1 mutation who are not eligible for standard treatment.

We continue to evaluate ivosidenib in the following clinical trials:

Phase 1b frontline combination trial (enasidenib is also being evaluated)

Ivosidenib is being evaluated in a phase 1b, multicenter, international, open-label clinical trial, conducted by us, to evaluate the safety and clinical activity of ivosidenib or enasidenib in combination with induction and consolidation therapy in patients with newly diagnosed AML with an IDH1 or IDH2 mutation who are eligible for intensive chemotherapy using a primary endpoint of safety and tolerability of ivosidenib or enasidenib when administered with induction and consolidation therapy. The trial enrollment is complete.

In December 2018, we presented interim data from this trial at the American Society of Hematology meeting in San Diego, California, or ASH 2018.

Phase 1/2 frontline combination trial (enasidenib is also being evaluated)

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

In June 2018, we presented new safety and efficacy data from this trial at the American Society of Clinical Oncology meeting in Chicago, Illinois, or ASCO 2018.

AGILE

Ivosidenib is being evaluated in AGILE, a global, registration-enabling phase 3 clinical trial, combining ivosidenib and VIDAZA® (azacitidine) in newly diagnosed AML patients with an IDH1 mutation who are ineligible for intensive chemotherapy. The trial is enrolling patients and we expect to complete enrollment in 2020.

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 enasidenib and standard induction and consolidation chemotherapy with a primary endpoint of event-free survival in frontline AML patients with an IDH1 or IDH2 mutation in the first quarter of 2019. The trial is expected to enroll approximately 500 patients with an IDH1 mutation and approximately 500 patients with an IDH2 mutation.

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 American Society of Clinical Oncology meeting in Chicago, Illinois. 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, or SNO 2017.

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 enrollment was completed in the first quarter of 2019. Assuming a positive trial result, we plan to submit a sNDA to the FDA for TIBSOVO® for second line or later IDH1 mutant-positive cholangiocarcinoma by the end of 2019.

The FDA granted us fast track designation for ivosidenib for treatment of patients with previously treated, unresectable or metastatic cholangiocarcinoma with an IDH1 mutation, and granted orphan drug designation for ivosidenib for the treatment of cholangiocarcinoma.

Enasidenib

Enasidenib is an orally available, selective, potent inhibitor of the mutated IDH2 protein, making it a highly targeted therapeutic candidate for the treatment of patients with cancers that harbor IDH2 mutations, including those with AML, who have a historically poor prognosis. In August 2017, the FDA granted Celgene approval of IDHIFA® for the treatment of adult patients with R/R AML and an IDH2 mutation. In June 2018, Celgene submitted an MAA to the EMA for IDHIFA® for IDH2 mutant-positive AML.

Celgene maintains worldwide development and commercial rights to enasidenib and will fund the future development and commercialization costs related to this program. In April 2010, we entered into a collaboration agreement with Celgene focused on cancer metabolism, or the 2010 Agreement. Under the remaining terms of the 2010 Agreement, Celgene is responsible for all development costs for enasidenib, and we are eligible to receive up to $80.0 million in potential milestone payments, which are comprised of: (i) up to $55.0 million in milestone payments upon achievement of specified ex-U.S. regulatory milestone events,

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of which $35.0 million relates to the first regulatory approval in any of China, Japan or a major European country, and (ii) a $25.0 million milestone payment upon achievement of a specified ex-U.S. commercial milestone event. Additionally, we are eligible to receive tiered royalties on any net sales of IDHIFA®.

In addition to the clinical trials discussed above, enasidenib is also being evaluated by Celgene in IDHENTIFY, an international phase 3, multi-center, open-label, randomized clinical trial designed to compare the efficacy and safety of enasidenib versus conventional care regimens in patients 60 years or older with IDH2 mutant-positive AML that is refractory to or relapsed after second- or third-line therapy. This trial is currently enrolling patients and we have not yet presented any clinical data from this trial.

Vorasidenib (AG-881): brain penetrant pan-IDH program

Vorasidenib (AG-881) is an orally available, selective, brain-penetrant, pan-IDH mutant inhibitor. We are currently focusing our development efforts for vorasidenib (AG-881) in glioma. In connection with the termination of the AG-881 Agreements discussed below, Celgene shall be eligible to receive royalties from us at a low single-digit percentage rate on worldwide net sales of products containing vorasidenib (AG-881).

Phase 1 clinical trial (advanced solid tumors)

We are conducting a phase 1 multi-center, open-label clinical trial of vorasidenib (AG-881) in patients with advanced IDH1 or IDH2 mutant-positive solid tumors, including glioma. The goal of this trial is to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and clinical activity of vorasidenib (AG-881) in advanced solid tumors. An maximum tolerated dose was established and enrollment in this trial is complete. In June 2018, we presented the first data from this trial at ASCO 2018.

In the first quarter of 2018, we initiated a perioperative study with ivosidenib and vorasidenib (AG-881) in low grade glioma to further investigate their effects on brain tumor tissue. As agreed with Celgene in connection with the termination of the AG-881 Agreements, Celgene continued to co-fund certain costs associated with the ongoing phase 1 clinical development of vorasidenib (AG-881) through December 31, 2018 and we funded the perioperative study ourselves as previously agreed with Celgene.

We expect to initiate a registration-enabling phase 3 study of vorasidenib (AG-881) in low-grade glioma with an IDH1 mutation by the end of 2019.

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 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 of PK deficiency, identify patients and treatment centers, and capture other clinical data, including genetic information. We initiated 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.

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Mitapivat: PK Activator

Mitapivat is an orally available small molecule and a potent activator of the wild-type (normal) and mutated PKR enzymes, which has resulted in restoration of ATP levels and a decrease in 2,3-diphosphoglycerate levels in blood sampled from patients with PK deficiency and treated ex-vivo with mitapivat. The wild-type PKR activity of mitapivat allowed us to study enzyme activation in healthy volunteers, providing an opportunity for us to understand the safety, dosing and pharmacodynamic activity of mitapivat prior to entering a proof-of-concept study in patients. We have worldwide development and commercial rights to mitapivat and expect to fund the future development and commercialization costs related to this program. The FDA granted orphan drug designation for mitapivat for treatment of patients with PK deficiency and granted fast track designation to mitapivat for the treatment of patients with PK deficiency. In December 2016, we announced our decision to advance mitapivat into pivotal development as the first potential disease-modifying treatment for PK deficiency.

DRIVE-PK

In June 2015, we initiated DRIVE PK, a global phase 2, first-in-patient, open-label safety and efficacy clinical trial of mitapivat in adult, transfusion-independent patients with PK deficiency. In June 2016, we reported the first clinical data from DRIVE PK at the 22nd Congress of the European Hematology Association establishing proof of concept for mitapivat. The trial reached target enrollment of 52 patients in November 2016, and in December 2017, we reported updated data from the trial at the American Society of Hematology meeting in San Diego, California.

ACTIVATE and ACTIVATE-T

In April 2018, we initiated ACTIVATE-T, a single arm, global, pivotal trial of mitapivat in approximately 20 regularly-transfused patients with PK deficiency. The primary endpoint of the ACTIVATE-T trial is a greater than 33% reduction in transfusion burden over a six-month period compared to the patient's transfusion history.

In June 2018, we initiated ACTIVATE, a 1:1 randomized, placebo-controlled, global, pivotal trial of mitapivat in approximately 80 patients with PK deficiency who do not receive regular transfusions. The primary endpoint of the ACTIVATE trial is the proportion of patients who achieve at least a 1.5 g/dL increase in hemoglobin sustained over multiple visits compared to placebo. We expect to complete enrollment of these trials in 2019.

Phase 2 clinical trial (thalassemia)

In December 2018, we initiated a phase 2, open-label safety and efficacy clinical trial of mitapivat in approximately 20 adult patients with non-transfusion-dependent thalassemia. The primary endpoint of the trial is the proportion of patients who achieve at least a 1.0 g/dL increase in hemoglobin levels at 12 weeks as compared to baseline hemoglobin levels. Patients in the trial will receive a twice-daily oral dose of mitapivat administered as a single agent at an initial dose of 50mg or 100mg for up to 24 weeks, with the goal of achieving proof-of-concept for mitapivat in this patient population by the end of 2019.

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

AG-270, an orally available selective potent inhibitor of MAT2A, is our development candidate focused on MTAP-deleted cancer. 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.

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.

In March 2018, we initiated a phase 1 dose-escalation trial of AG-270 in multiple tumor types carrying an MTAP deletion. The purpose of this phase 1 multi-center, open-label study is to evaluate the safety, pharmacokinetics, pharmacodynamics and clinical activity of AG-270 in approximately 50 patients with advanced solid tumors or lymphoma with an MTAP deletion. AG-270 is administered as a single agent dosed orally once daily in 28-day cycles. The first part of the trial is a dose-escalation phase in which cohorts of patients will receive ascending doses of

AG-270 to determine the pharmacokinetics, pharmacodynamics and optimal dose. The second part of the trial is a dose expansion phase where additional patients will receive AG-270 at the optimal dose to further evaluate its safety, tolerability and clinical activity as a potential dose for future studies. We expect to complete dose escalation and initiate two dose expansion arms of this trial in the first half of 2019; one as a single agent in a variety of MTAP-deleted cancers and the second in a solid tumor in combination with standard of care.

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AG-636: Targeting DHODH for the treatment of hematologic malignancies

In October 2018, we submitted an IND for AG-636, an inhibitor of DHODH, licensed by us from Aurigene Discovery Technologies Limited, or Aurigene, for the treatment of hematologic malignancies. The IND was accepted by the FDA in November 2018.

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.

We plan to initiate a phase 1 clinical trial of AG-636 in lymphoma in the first half of 2019.

Collaborations with Celgene

2016 Agreement

In May 2016, we entered into the 2016 Agreement focused on 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. 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, an inhibitor of MAT2A, will now be governed by the 2016 Agreement.

During the research term of the 2016 Agreement, we plan to conduct research programs focused on discovering compounds that are active against metabolic targets in the immuno-oncology, or IO, field. The initial four-year research term will expire on May 17, 2020, 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.

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

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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, 2018, 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.

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

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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 were directed to both the IDH1 target and the IDH2 target.

Termination of AG-881 Agreements

In September 2018, we and Celgene agreed to terminate our joint worldwide collaboration focused on the development and commercialization of vorasidenib (AG-881) products, or the AG-881 Agreements, effective as of September 4, 2018. From and after September 4, 2018, we obtained sole global rights to vorasidenib (AG-881). Neither we nor Celgene will have any further financial obligation under the AG-881 Agreements, including milestones, royalties or other payments, except that (a) Celgene shall be eligible to receive royalties from us at a low single-digit percentage rate on worldwide net sales of products containing vorasidenib (AG-881) and (b) we and Celgene shall split certain agreed-upon worldwide development costs for vorasidenib (AG-881) until December 31, 2018. In addition, for a specified period and subject to specified exceptions, Celgene and its affiliates shall be prohibited from developing, manufacturing or commercializing any product that inhibits IDH1 at specified levels of binding for any indication and we shall be prohibited from developing, manufacturing or commercializing vorasidenib (AG-881) in hematologic indications.

2010 Agreement

The 2010 Agreement, which was entered into in April 2010, 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 $80.0 million in potential milestone payments for the IDHIFA® program. The potential milestone payments are comprised of: (i) up to $55.0 million in milestone payments upon achievement of specified ex-U.S. regulatory milestone events, of which $35.0 million relates to the first regulatory approval in any of China, Japan or a major European country, 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, 2018, we earned $7.2 million in royalty revenue under the 2010 Agreement.

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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.

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.

CStone Agreement

In June 2018, we entered into the CStone Agreement for the development and commercialization of certain products containing ivosidenib in mainland China, Hong Kong, Macau, and Taiwan for therapeutic uses in humans, excluding brain cancer, unless later adopted by us in our sole discretion. We retain development and commercialization rights for the rest of the world.

Pursuant to the CStone Agreement, CStone will initially be responsible for the development and commercialization of ivosidenib in AML and cholangiocarcinoma, as well as other indications that the parties mutually agree to in the future. CStone will also be responsible, at our discretion, for the development and commercialization of ivosidenib in brain cancer indications. We granted CStone specified intellectual property licenses to enable CStone to perform its obligations and exercise its rights under the CStone Agreement, including license grants to enable CStone to conduct development and commercialization activities pursuant to the terms of the CStone Agreement.

CStone is responsible for all costs it incurs in developing, obtaining regulatory approval of, and commercializing ivosidenib in China, Hong Kong, Macau, and Taiwan, as well as certain costs incurred by us.

During the term of the CStone Agreement, each party and its affiliates are prohibited from developing or commercializing any other compound or product that inhibits IDH1 mutations at specified levels of binding, in the case of CStone, anywhere in the world, and in the case of us, in China, Hong Kong, Macau, and Taiwan. Subject to specified exceptions, CStone and its affiliates are also prohibited from developing or commercializing certain other compounds or products that directly or indirectly treat AML, cholangiocarcinoma or, if applicable, glioma in patients that have an IDH1 mutation.

The CStone Agreement contemplates that we will enter into ancillary arrangements with CStone, including clinical and commercial supply agreements and a pharmacovigilance agreement.

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, or collaborate with third parties to file, patent applications directed to our key product candidates, including TIBSOVO® (ivosidenib), IDHIFA® (enasidenib), AG-881 (vorasidenib), mitapivat, AG-270 and AG-636, 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 February 1, 2019 we owned or licensed approximately 24 issued U.S. patents, 268 issued foreign patents, 32 pending

U.S. patent applications, 303 pending foreign patent applications, and 13 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.

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The intellectual property portfolios for our most advanced programs as of February 1, 2019 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 TIBSOVO® (ivosidenib), IDHIFA® (enasidenib), and AG-881 (vorasidenib), as well as analogs thereof, methods of use, various solid state forms of these compounds and diagnostic methods for detecting various IDH1 and IDH2 mutations. As of February 1, 2019, we owned approximately 15 issued U.S. patents, 110 issued foreign patents, 18 pending U.S. patent applications, 230 pending foreign patent applications in a number of jurisdictions, and 5 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 2038. Patent term adjustments or patent term extensions could result in later expiration dates.

PK activator program

The intellectual property portfolio for our PK activator program contains patent applications directed to compositions of matter for mitapivat, as well as analogs thereof, various solid state forms of mitapivat and compositions of matter for second generation PKR activators, as well as methods of use for these novel compounds. As of February 1, 2019, we owned approximately 5 issued U.S. patents, 110 issued foreign patents, 4 pending U.S. patent applications, 46 pending foreign patent applications in a number of jurisdictions, and 2 pending PCT patent applications, directed to our PK activator program, including our product candidate. The patents that have issued or will issue for our PK activator program will have a statutory expiration date of at least 2030 to 2038. 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 February 1, 2019, we owned approximately 5 pending U.S. patent applications, 12 pending foreign patent applications, and 3 pending PCT patent applications, directed to 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 to 2039. Patent term adjustments or patent term extensions could result in later expiration dates.

DHODH inhibitor program

The intellectual property portfolio for our DHODH inhibitor program contains patents and patent applications, exclusively licensed to us by Aurigene, directed to compositions of matter for AG-636, as well as analogs thereof and other compound families, as well as methods of use for these novel compounds. The intellectual property portfolio for our DHODH inhibitor program further contains patent applications, assigned solely to Agios, that are directed to solid state forms of AG-636 and methods of use for these forms of AG-636, and other methods of use for AG-636. As of February 1, 2019, we exclusively licensed or independently filed approximately 4 issued U.S. patents, 48 issued foreign patents, 5 pending U.S. patent applications, 15 pending foreign patent applications, and 3 pending PCT patent applications directed to our DHODH inhibitor program. The patents that have issued or will issue for our DHODH inhibitor program will have a statutory expiration date of at least 2030 to 2039. 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, although term extensions may be available. 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. The extension of the term of foreign patents varies, in accordance with local law. Although certain of the patents granted by the regulatory authorities of the EU may expire at specific dates, the terms of patents granted in certain European countries may

extend beyond such EU patent expiration date if we were to obtain a supplementary protection certificate.

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.

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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, third-party service providers, 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 Abbvie Inc., ASLAN Pharmaceuticals Limited; AstraZeneca Plc.; Astellas Pharma Inc.; Bayer AG; Clear Creek Bio; Daiichi Sankyo Company, Ltd.; Eli Lilly and Company; Forma Therapeutics Holdings, LLC; GlaxoSmithKline plc; Jazz Pharmaceuticals plc; Merck & Co.; Novartis International AG; Pfizer, Inc.; and Roche Holdings, Inc. and its subsidiary Genentech, Inc. In the MIO field, our principal competitors include AstraZeneca; BeiGene Ltd.; Bristol-Myers Squibb Company; GlaxoSmithKline; Genentech; and Merck. 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. For example, other than TIBSOVO® and IDHIFA®, recently-approved treatments for AML include Venclexta® from Abbvie (in collaboration with Roche); Xospata® from Astellas; Rydapt® from Novartis; Vyxeos® from Jazz; and Daurismo® and Mylotarg® from Pfizer. In some cases, these drugs are administered in combination to enhance efficacy. While our products and 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 may 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, including immuno-oncology therapies in clinical development to treat cancer. 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, and ASLAN and Clear Creek Bio are conducting clinical trials of their DHODH inhibitors

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ASLAN003 and Brequinar, respectively, in AML. 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.

Rare genetic diseases. In the field of RGDs, our principal competitors include Acceleron Pharma Inc.; BioMarin Pharmaceutical, Inc.; bluebird bio, Inc.; Novartis; Pfizer; and Rocket Pharma LTD.

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 may not be competitive with them. In addition to currently marketed therapies, there are also a number of products that are either small molecules, 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 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, or other branded 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 ivosidenib, enasidenib, vorasidenib (AG-881), mitapivat, AG-270 and AG-636 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 TIBSOVO®, we primarily obtain our 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 TIBSOVO®, 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.

Ivosidenib, enasidenib, vorasidenib (AG-881), mitapivat, AG-270 and AG-636 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 expect to rely on third parties for the manufacture and sale of any companion diagnostics we develop.

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Government Regulation and Product Approvals

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions, including the EU, extensively regulate, among other things, the research, development, testing, manufacture, pricing, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of biopharmaceutical products. The processes for obtaining marketing approvals in the United States and in foreign countries and jurisdictions, along with compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

Approval and Regulation of Drugs in the United States

In the United States, drug products are regulated under the Federal Food, Drug and Cosmetic Act, or FDCA, and applicable implementing regulations and guidance. The failure of an applicant to comply with the applicable regulatory requirements at any time during the product development process, including non-clinical testing, clinical testing, the approval process or post-approval process, may result in delays to the conduct of a study, regulatory review and approval and/or administrative or judicial sanctions. These sanctions may include, but are not limited to, the FDA's refusal to allow an applicant to proceed with clinical trials, refusal to approve pending applications, license suspension or revocation, withdrawal of an approval, warning letters, adverse publicity, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines and civil or criminal investigations and penalties brought by the FDA or Department of Justice, or DOJ, or other government entities, including state agencies.

An applicant seeking approval to market and distribute a new drug in the United States generally must satisfactorily complete each of the following steps before the product candidate will be approved by the FDA:

•preclinical testing including laboratory tests, animal studies and formulation studies which must be performed in accordance with the FDA's good laboratory practice, or GLP, regulations and standards;

•submission to the FDA of an IND for human clinical testing, which must become effective 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 to establish the safety, potency and purity of the product candidate for each proposed indication, in accordance with current good clinical practices, or GCP;

•preparation and submission to the FDA of a new drug application, or NDA, for a drug product which includes not only the results of the clinical trials, but also, detailed information on the chemistry, manufacture and quality controls for the product candidate and proposed labeling for one or more proposed indication(s);

•review of the product candidate by an FDA advisory committee, where appropriate or if applicable;

•satisfactory completion of FDA inspection of the manufacturing facility or facilities, including those of third parties, at which the product candidate or components thereof are manufactured 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 any FDA audits of the non-clinical and clinical trial sites to assure compliance with GCP and the integrity of clinical data in support of the NDA;

•payment of user fees and securing FDA approval of the NDA to allow marketing of the new drug product; and

•compliance with any post-approval requirements, including the potential requirement to implement a REMS and the potential requirement to conduct any post-approval studies required by the FDA.

Preclinical Studies

Before an applicant begins testing a product candidate with potential therapeutic value in humans, the product candidate enters the preclinical testing stage. Preclinical tests include laboratory evaluations of product chemistry, formulation and stability, as well as other studies to evaluate, among other things, the toxicity of the product candidate. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements, including GLP regulations and standards. The results of the preclinical tests, together with manufacturing information and analytical data, 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, and long-term toxicity

studies, may continue after the IND is submitted.

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The IND and IRB Processes

An IND is an exemption from the FDCA that allows an unapproved product candidate to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer such investigational product to humans. Such authorization must be secured prior to interstate shipment and administration of any product candidate 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, must be 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, or thereafter, the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold or partial 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 a foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with certain regulatory requirements of the FDA in order to use the study as support for an IND or application for marketing approval. Specifically, on April 28, 2008, the FDA amended its regulations governing the acceptance of foreign clinical studies not conducted under an investigational new drug application as support for an IND or a new drug application. The final rule provides that such studies must be conducted in accordance with GCP, including review and approval by an independent ethics committee 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 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 as to 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 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 clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on its ClinicalTrials.gov website.

Expanded Access to an Investigational Drug for Treatment Use

Expanded access, sometimes called "compassionate use," is the use of investigational new drug products outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options. The rules and regulations related to expanded access are intended to improve access to investigational drugs for patients who may benefit from investigational therapies. FDA regulations allow access to investigational drugs under an IND by the company or the treating physician for treatment purposes on a case-by-case basis for: individual patients (single-patient IND applications for treatment in emergency settings and non-emergency settings);

intermediate-size patient populations; and larger populations for use of the drug under a treatment protocol or Treatment IND Application.

When considering an IND application for expanded access to an investigational product with the purpose of treating a patient or a group of patients, the sponsor and treating physicians or investigators will determine suitability when all of the following criteria apply: patient(s) have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; the potential patient benefit justifies the potential risks of the treatment and the potential risks are not unreasonable in the context or condition to be treated; and the expanded use of the investigational drug for the requested treatment will not interfere initiation, conduct, or completion of clinical investigations that could support marketing approval of the product or otherwise compromise the potential development of the product.

Human clinical trials in support of an NDA

Clinical trials involve the administration of the investigational product candidate to human subjects under the supervision of a qualified investigator 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 clinical trial protocols detailing, among other things, the objectives of the study, inclusion and exclusion criteria, 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, but the phases may overlap or be combined. Additional studies may also be required after approval.

Phase 1 clinical trials are initially conducted in a limited population to test the product candidate for safety, including adverse effects, dose tolerance, absorption, metabolism, distribution, excretion and pharmacodynamics in healthy humans or in patients. During Phase 1 clinical trials, information about the investigational drug product's pharmacokinetics and pharmacological effects may be obtained to permit the design of well-controlled and scientifically valid Phase 2 clinical trials.

Phase 2 clinical trials are generally conducted in a limited patient population to identify possible adverse effects and safety risks, evaluate the efficacy of the product candidate for specific targeted indications and determine dose tolerance and optimal dosage. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more costly Phase 3 clinical trials. Phase 2 clinical trials are well controlled, closely monitored and conducted in a limited patient population.

Phase 3 clinical trials proceed if the Phase 2 clinical trials demonstrate that a dose range of the product candidate is potentially effective and has an acceptable safety profile. Phase 3 clinical trials are undertaken within an expanded patient population to further evaluate dosage, provide substantial evidence of clinical efficacy and further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial sites. A well-controlled, statistically robust Phase 3 clinical trial may be designed to deliver the data that regulatory authorities will use to decide whether or not to approve, and, if approved, how to appropriately label a drug: such Phase 3 studies are referred to as "pivotal."

In some cases, the FDA may approve an NDA for a product candidate but require the sponsor to conduct additional clinical trials to further assess the product candidate's safety and effectiveness after approval. Such post-approval trials are typically referred to as Phase 4 clinical trials. These studies are used to gain additional experience from the treatment of a larger number of patients in the intended treatment group and to further document a clinical benefit in the case of drugs approved under accelerated approval regulations. Failure to exhibit due diligence with regard to conducting Phase 4 clinical trials could result in withdrawal of approval for products.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the product; 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 product 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.

Review and Approval of an NDA

In order to obtain approval to market a drug product in the United States, a marketing application must be submitted to the FDA that provides sufficient data establishing the safety, purity and potency of the proposed drug product for its intended indication.

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The application includes all relevant data available from pertinent preclinical and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls and proposed labeling, among other things. Data can come from company-sponsored clinical trials intended to test the safety and effectiveness of a use of a product, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety, purity and potency of the drug product to the satisfaction of the FDA.

The NDA is a vehicle through which applicants formally propose that the FDA approve a new product for marketing and sale in the United States for one or more indications. Every new drug product candidate must be the subject of an approved NDA before it may be commercialized in the United States. Under federal law, the submission of most NDAs is subject to an application user fee, which for federal fiscal year 2019 is $2,588,478 for an application requiring clinical data. The sponsor of an approved NDA is also subject to an annual program fee, which for fiscal year 2019 is $309,915 Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for products with orphan designation and a waiver for certain small businesses.

Following submission of an NDA, the FDA conducts a preliminary review of the application generally within 60 calendar days of its receipt and strives to inform the sponsor by the 74th day after the FDA's receipt of the submission whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept the application for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA has agreed to specified performance goals in the review process of NDAs. Under that agreement, 90% of applications seeking approval of New Molecular Entities, or NMEs, are meant to be reviewed within ten months from the date on which the FDA accepts the application for filing, and 90% of applications for NMEs that have been designated for "priority review" are meant to be reviewed within six months of the filing date. For applications seeking approval of products that are not NMEs, the ten-month and six-month review periods run from the date that the FDA receives the application. The review process and the Prescription Drug User Fee Act goal date may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an application, 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 component manufacturing, finished 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. Under the FDA Reauthorization Act of 2017, the FDA must implement a protocol to expedite review of responses to inspection reports pertaining to certain applications, including applications for products in shortage or those 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.

The FDA may refer an application for a novel product 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

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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 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.

With passage of the 21st Century Cures Act, or the 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 that is intended to treat, modify, reverse or cure a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product 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 product for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. Products granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

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

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a product, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the

development and approval of products for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit. Thus, the benefit of accelerated approval derives from the potential to receive approval based on surrogate endpoints sooner than possible for trials with clinical or survival endpoints, rather than deriving from any explicit shortening of the FDA approval timeline, as is the case with priority review.

The accelerated approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the product's clinical benefit. As a result, a product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or

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confirm a clinical benefit during post-marketing studies, would allow the FDA to initiate expedited proceedings to withdraw approval of the product. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

Real-Time Oncology Review of Supplemental NDAs

Through its Oncology Center for Excellence, the FDA has established two pilot programs allowing for real-time review of supplemental drug applications for previously approved oncology products. This approach will allow FDA to evaluate clinical data as soon as the results of a clinical trial become available with the objective of reviewing and approving a new indication soon after an applicant files the supplemental NDA. The first of these pilot programs, Real-Time Oncology Review, or RTOR, focuses on early submission of data that are the most relevant to assessing the product's safety and effectiveness. RTOR allows the FDA to review much of the data earlier, after the clinical trial results become available and the database is locked, but before the information is formally submitted to the agency The FDA has established several criteria to be determine whether a supplemental NDA may be selected for RTOR. Those criteria include whether: the drug is likely to demonstrate substantial improvements over available therapy; the study design is straight forward, as determined by the review division and the OCE; the endpoints can be easily interpreted. Supplemental NDAs with chemistry, manufacturing and control formulation changes and supplements with pharmacology/ toxicology data are excluded from RTOR. In addition, submissions with greater complexity, including those with companion diagnostics, may also be excluded for the purposes of the pilot program. On the basis of these criteria, the appropriate FDA review division and OCE management will jointly decide whether the application can be selected for the RTOR pilot program.

If FDA determines that RTOR is an appropriate review pathway, the applicant can send pre-submission data to the agency under the original NDA two to four weeks after all patient data have been entered and locked in the database and the applicant is ready to request FDA approval. The package should also include key raw and derived datasets, including safety/efficacy tables and figures, study protocol and amendments, and a draft of the package insert. The applicant must also submit key results, analysis, and datasets for other disciplines, if applicable. The FDA will then evaluate these materials for sufficiency and integrity so that it can analyze the data to properly address key regulatory questions. By the time the applicant submits the application to the FDA, the review team will have completed the analysis and be familiar with the data, and can conduct a more efficient, timely, and thorough review.

The FDA's Decision on an NDA

On the basis of the FDA's evaluation of the application 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 new product, it may limit the approved indications for use of the product. The agency may also 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, to help ensure that the benefits of the product outweigh the potential risks. REMS can include medication guides, communication plans for health care professionals, and elements to assure safe use, or ETASU. ETASU can 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 patent registries. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Regulation

If regulatory approval for marketing of a product or new indication for an existing product is obtained, the sponsor will be required to comply with all regular post-approval regulatory requirements as well as any post-approval

requirements that the FDA may have imposed as part of the approval process. The sponsor will be required to report, among other things, certain adverse reactions and manufacturing problems to the FDA, provide updated safety and efficacy information and comply with requirements concerning advertising and promotional labeling requirements. Manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMP regulations, which impose certain procedural and documentation requirements upon manufacturers. Accordingly, the sponsor

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and its third-party manufacturers must continue to expend time, money and effort in the areas of production and quality control to maintain compliance with cGMP regulations and other regulatory requirements.

A product may also be subject to official lot release, meaning that the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release, the manufacturer must submit samples of each lot, together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot, to the FDA. The FDA may in addition perform certain confirmatory tests on lots of some products before releasing the lots for distribution.

Finally, the FDA will conduct laboratory research related to the safety, purity, potency and effectiveness of pharmaceutical products.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements 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 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 applications or supplements to approved applications, or suspension or revocation of product license approvals;

•product seizure or detention, or refusal to permit the import or export of products; or

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

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 for the proposed use. 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

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

Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, the strength of the drug and the conditions of use of the drug. At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug. Under the statute, a generic drug is bioequivalent to a RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug." Upon approval of an ANDA, the FDA indicates whether the generic product is "therapeutically equivalent" to the RLD in its publication "Approved Drug Products with Therapeutic Equivalence Evaluations," also referred to as the "Orange Book." Physicians and pharmacists consider a therapeutic equivalent generic drug to be fully substitutable for the RLD. In addition, by operation of certain state laws and numerous health insurance programs, the FDA's designation of therapeutic equivalence often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.

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

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

of data exclusivity shortly before a product is approved.

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 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 application will not be approved until all the listed patents claiming the referenced product have expired (other than method of use patents involving indications for which the applicant is not seeking approval).

If the ANDA 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 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. 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, FDA will meet early in the development process to discuss pediatric study plans with sponsors and FDA must meet with 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 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.

The FDA Reauthorization Act of 2017 established new requirements to govern certain molecularly targeted cancer indications. Any company that submits an NDA three years after the date of enactment of that statute must submit pediatric assessments

with the NDA if the drug is intended for the treatment of an adult cancer and is directed at a molecular target that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer. The investigation must be designed to yield clinically meaningful pediatric study data regarding the dosing, safety and preliminary efficacy to inform pediatric labeling for the product.

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

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 product available in the United States for treatment of the disease or condition will be recovered from sales of the product. A company must seek orphan drug designation before submitting an NDA for the candidate product. If the request is granted, the FDA will disclose the identity of the therapeutic agent and its potential use. Orphan drug designation does not shorten the PDUFA goal dates for the regulatory review and approval process, although it does convey certain advantages such as tax benefits and exemption from the PDUFA application fee.

If a product with orphan designation receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the product generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve another sponsor's marketing application for the same drug for the same condition for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different product for the same rare disease or condition, nor does it block the approval of the same product for different conditions. If a drug designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity.

Orphan drug exclusivity will not bar approval of another product under certain circumstances, including if a subsequent product with the same drug for the same condition 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. This is the case despite an earlier court opinion 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 on a patent covering a product is typically one-half the time between the effective date of a clinical investigation involving human beings is begun and the submission date of an application, plus the time between the submission date of an application 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 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 products 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.

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

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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, 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 a manufacturer fails to comply with applicable regulatory requirements.

Health care Law and Regulation

Health care providers and third-party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with providers, consultants, third-party payors and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, patient privacy laws and regulations and other health care laws and regulations that may constrain business and/or financial arrangements. Restrictions under applicable federal and state health care 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, paying, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal health care program such as Medicare

and Medicaid;

•the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false, fictitious or fraudulent or knowingly making, using or causing to made or used a false record or statement to avoid, decrease or conceal an obligation to pay money to the federal government.

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•the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal laws that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any health care benefit program or making false statements relating to health care matters;

• HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

•the federal false statements statute, which prohibits knowingly and willfully falsifying, concealing ·or covering up a material fact or making any materially false statement in connection with the delivery of or payment for health care benefits, items or services;

•the Foreign Corrupt Practices Act, or FCPA, which prohibits companies and their intermediaries from making, or offering or promising to make improper payments to non-U.S. officials for the purpose of obtaining or retaining business or otherwise seeking favorable treatment;

•the federal transparency requirements known as the federal Physician Payments Sunshine Act, under the Patient Protection and Affordable Care Act, as amended by the Health Care Education Reconciliation Act, or the Affordable Care Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies to report annually to the Centers for Medicare & Medicaid Services, or CMS, within the United States Department of Health and Human Services, information related to payments and other transfers of value made by that entity to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; and

•analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, which may apply to health care items or services that are reimbursed by non-government third-party payors, including private insurers.

Further, 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 manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures. Additionally, some state and local laws require the registration of pharmaceutical sales representatives in the jurisdiction. 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.

Pharmaceutical Insurance Coverage and Health Care Reform

In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payors to reimburse all or part of the associated health care costs. Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Thus, even if a product candidate is approved, sales of the product 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, the product. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors are increasingly challenging the prices charged, examining the medical necessity and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payors may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the approved products for a particular indication.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable marketing approvals. Nonetheless, product candidates may not be considered medically necessary or cost effective. A decision by a third-party payor not to cover a product could reduce physician utilization once the product is approved and have a material adverse effect on sales, results of operations and financial condition. Additionally, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor.

The containment of health care costs also has become a priority of federal, state and foreign governments and the prices of products 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

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existing controls and measures, could further limit a company's revenue generated from the sale of any approved products. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive marketing approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

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 biologics and other medical products, government control and other changes to the health care system in the United States.

In March 2010, the United States Congress enacted the Affordable Care Act, or ACA, which, among other things, includes changes to the coverage and payment for drug products under government health care programs. Among the provisions of the ACA of importance to our potential product 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;

• 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 li