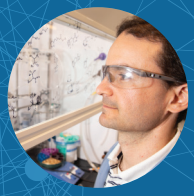
2019 ANNUAL REPORT

agios

THE OTHER SIDE OF POSSIBLE



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2019 ANNUAL REPORT

MEET **MOLLY**

Molly was diagnosed with pyruvate kinase (PK) deficiency when she was 9 months old. She's a part-time gymnastics coach and loves backyard bonfires and making s'mores with her family. She went to school to be a nurse but hasn't been able to practice because of the toll PK deficiency takes on her body and the debilitating fatigue she deals with every day. She is dependent on regular transfusions and has undergone countless surgeries to manage her condition. PK deficiency has a significant impact on her daily living, relationships and career. She continues to advocate for improved understanding of PK deficiency and hope for better treatment options.

Agios is proud to work toward improving the lives of people like Molly.

FELLOW **STOCKHOLDERS**

As I reflect on my first full year as CEO of Agios, I have more confidence than ever in the quality of our science, the strength of our team, our differentiated portfolio of preclinical, clinical and commercial programs and our potential to meaningfully improve the lives of people with hematologic malignancies, solid tumors and rare genetic diseases.

A NEW CHAPTER OF **INNOVATION**

In our first 10+ years, we completed a full cycle of innovation, having advanced two precision oncology medications based on our pioneering work with isocitrate dehydrogenase (IDH) inhibitors—IDHIFA® (enasidenib) and TIBSOVO® (ivosidenib tablets)—from discovery in our own labs, through clinical development and into the hands of IDH mutant acute myeloid leukemia (AML) patients in need. During that same period, we developed and discovered six additional investigational new drug (IND) candidates and fostered a productive research engine that continues to yield promising preclinical molecules and new therapeutic approaches.

We will leverage the expertise and learnings from our first decade of success as we begin a new chapter for Agios by advancing our first late-stage rare genetic disease molecule, the pyruvate kinase-R (PKR) activator mitapivat, across three opportunities in pyruvate kinase (PK) deficiency, thalassemia and sickle cell disease. We are also continuing our work on IDH inhibitors, expanding that franchise into solid tumors as well as to additional indications in hematologic malignancies.

Based on the strength of our existing clinical and late-stage preclinical programs, we have line of sight to value-generating milestones each year for the foreseeable future. Because of this, we recently unveiled our **Agios 2025 strategic vision**, sharing for the first time how we believe the company will evolve as our portfolio progresses. By the end of 2025, we expect:

- **4 marketed medicines** discovered and developed at Agios
- Approvals in **8+ indications** spanning hematologic malignancies, solid tumors and rare genetic diseases
- **6+ molecules in the clinic** generated by our internal research discovery engine
- **Cash-flow positivity** within the six-year timeframe

My confidence in our ability to achieve this vision is bolstered by my confidence in our people. The work we do is incredibly important, meaningful work—and each and every person who works at Agios is driven to think big and push just beyond their comfort zones. Trusting each other has been a key, proven element of our team dynamic throughout our existence, and it will continue to be central as we execute on this strategic vision.

2019: BUILDING THE FOUNDATION

This long-term vision is built on the foundation of our 2019 achievements. Some highlights of the year included:

Malignant Hematology

- Achieved approval of our **supplemental New Drug Application (sNDA)** for TIBSOVO® as a treatment for newly diagnosed patients with IDH1 mutant AML
- Received **two Breakthrough Therapy Designations for TIBSOVO®**: (1) in combination with azacitidine for the treatment of newly diagnosed AML patients with an IDH1 mutation who are ineligible for intensive chemotherapy, and (2) for the treatment of relapsed or refractory myelodysplastic syndrome (MDS) patients with an IDH1 mutation
- Initiated the **Phase 1 dose-escalation trial of AG-636**, an inhibitor of the metabolic enzyme dihydroorotate dehydrogenase (DHODH), in advanced lymphoma

Solid Tumors

- Announced **positive data from our first Phase 3 trial**, ClarIDHy, evaluating TIBSOVO® as a treatment for previously treated patients with IDH1 mutant cholangiocarcinoma
- **Initiated the Phase 3 INDIGO study of vorasidenib**, our brain-penetrant pan-IDH inhibitor, in patients with Grade 2 non-enhancing glioma with an IDH mutation
- Presented the first data from a **Phase 1 study of AG-270** in methylthioadenosine phosphorylase (MTAP)-deleted tumors; initiated combination arms of the Phase 1 study evaluating AG-270 in combination with taxanes in non-small cell lung cancer and pancreatic cancer

Rare Genetic Diseases

- Established proof-of-concept for mitapivat in **non-transfusion-dependent thalassemia** based on preliminary Phase 2 results
- Advanced pivotal trials evaluating mitapivat as a treatment for patients with **PK deficiency**, completing enrollment of the Phase 3 ACTIVATE-T study and nearly completing enrollment of the Phase 3 ACTIVATE study

Corporate

- Strengthened the Agios leadership team with several **key leadership appointments**, including Bruce Car as chief scientific officer; Jonathan Biller as chief legal officer; Orlando Oliveira as senior vice president and general manager, international; and Darrin Miles as senior vice president, U.S. commercial and global marketing
- Opened our **EU headquarters** in Zug, Switzerland

2020 OUTLOOK

As I'm writing this—just a few months into 2020—Agios is part of the global community that is grappling with the rapid and unpredictable outbreak of the SARS-CoV-2 virus. While this pandemic has impacted each of our lives both personally and professionally, we're prioritizing the health and wellbeing of our employees and their families, our communities and the patients we serve. The teamwork and resilience I've witnessed in these last few weeks has truly been remarkable and gives me hope and comfort as we face the uncertainty that lies ahead.

At the beginning of the year, we shared our ambitious 2020 priorities aimed at enabling us to meet or exceed our 2025 vision. The impact of the pandemic on these milestones remains to be seen, but we are actively working on creative, thoughtful ways to minimize the long-term implications for each of our programs so that we can continue our mission of delivering new medicines to patients.

This year will be pivotal for our first **rare genetic disease program,** with important milestones across three different hemolytic anemias. We expect to announce topline results from our two Phase 3 trials evaluating mitapivat in adults with PK deficiency. In anticipation of a potential U.S. approval for this indication, our commercial and medical affairs teams are ramping up pre-launch efforts, including educating patients and the healthcare community about this serious chronic anemia and raising awareness about the importance of diagnosis and testing. In addition, we are focused on expanding the clinical application of mitapivat into thalassemia and sickle cell disease, and we hope to share clinical data in both diseases this year.

2020 will also be a year of significant momentum for our **malignant hematology focus area.** We saw strong continued growth of TIBSOVO® use in both newly diagnosed and relapsed or refractory AML patients heading into the new year. Today, we're focused on

providing an uninterrupted supply of TIBSOVO® to patients despite the COVID-19 outbreak and continued access to our myAgios™ Patient Support Services.

We are working to expand the impact of TIBSOVO® to additional patients through both indication and geographic expansion. We are advancing three ongoing registration-enabling studies: the Phase 3 AGILE trial of TIBSOVO® in combination with azacitidine in frontline AML, the Phase 3 trial of TIBSOVO® in combination with intensive chemotherapy in frontline AML and the relapsed or refractory myelodysplastic syndrome arm of the TIBSOVO® Phase 1 study. In addition, we are working with European regulators on the potential approval of TIBSOVO® in relapsed or refractory AML.

Beyond these malignant hematology opportunities, we are also excited about the potential of IDH inhibition to improve the lives of patients with **solid tumors.** We anticipate filing an sNDA for TIBSOVO® in previously treated cholangiocarcinoma based on a mature overall survival data readout, and we are focused on enrolling the Phase 3 INDIGO trial of vorasidenib in patients with low-grade glioma.

We will continue to invest in our long-term future by advancing the work of our highly productive research engine. We received our eighth IND clearance in March and currently have more than 15 preclinical programs.

And we'll continue to invest in our people—each of whom believes in the importance of our work and in each other. We've made it clear to each employee that during the COVID-19 pandemic, we are not operating in "business as usual" circumstances, and we're here to support them throughout these uncertain times. No matter what, we're driven by a culture where people strive to be their best selves, connect with each other and welcome different perspectives and backgrounds. From early research to commercialization, we'll continue to focus on delivering for patients in need.

Before I close, I would like to take this opportunity to thank Drs. David Schenkein, our CEO from 2009 to February 1, 2019 and Scott Biller, our Chief Scientific Officer from 2010 to December 31, 2019, for their invaluable contributions over their many years of service with Agios. They were instrumental in creating the amazing company I now have the privilege of leading into its second decade.

I am grateful to our employees, scientific and clinical collaborators, founders, board members and stockholders for their continued support as we make important progress toward realizing our goal of making a difference in patients' lives. Most importantly, I want to thank the patients and their caregivers, nurses and physicians who participate in our clinical trials; without their support, our work and vision for the future could not move forward. Together, we can achieve the other side of possible.

Jacqualyn Fouse, Ph.D.
Chief Executive Officer

THREE FOCUS AREAS

For more than a decade, our mission has been to create differentiated, small molecule medicines for patients in three focus areas—malignant hematology, solid tumors and rare genetic diseases—based on our unique expertise in cellular metabolism and adjacent areas of biology.

1 MALIGNANT HEMATOLOGY

- acute myeloid leukemia
- myelodysplastic syndrome
- lymphoma

2 SOLID TUMORS

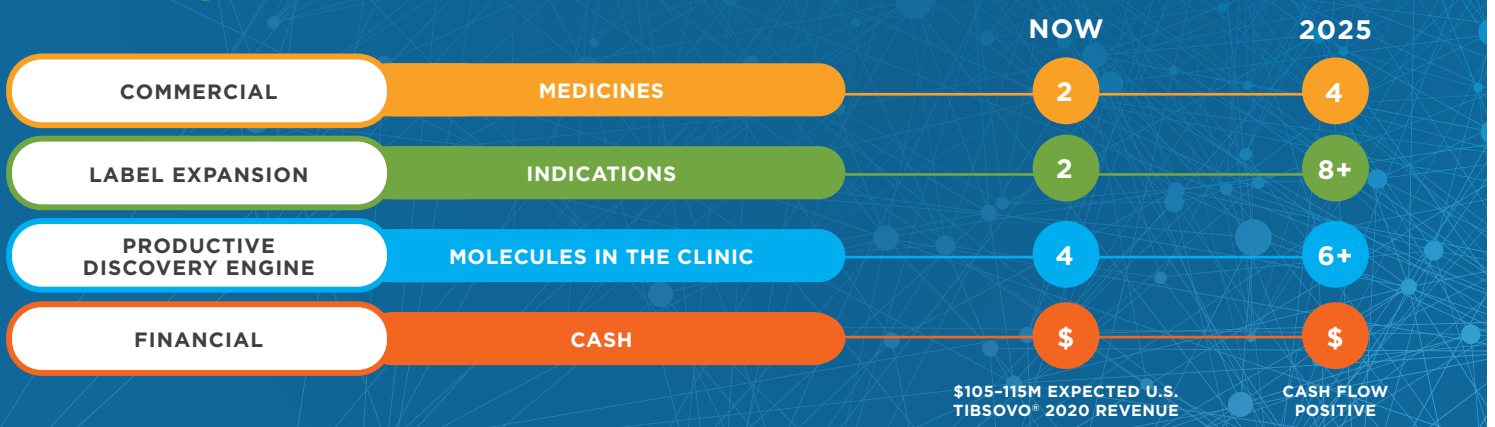
- cholangiocarcinoma
- low-grade glioma
- MTAP-deleted non-small cell lung cancer
- MTAP-deleted pancreatic cancer

3 RARE GENETIC DISEASES

- adult pyruvate kinase deficiency
- pediatric pyruvate kinase deficiency
- β- and α- thalassemia
- sickle cell disease

2025 VISION

Focused Innovation. Ambitious Development.
Transformative Treatments for Patients Across Three Focus Areas.



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, 2019

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	Trading symbol(s)	Name of Exchange on Which Registered
Common Stock, Par Value $0.001 per share	**AGIO**	**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 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 28, 2019 (based on the last reported sale price on the Nasdaq Global Select Market as of such date) was $2,563,418,196.

As of February 13, 2020, there were 68,513,573 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 2020 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, 2019 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," "goal," "intend," "may," "plan," "predict," "project," "strategy," "target," "potential," "will," "would," "could," "should," "continue," "vision" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this Annual Report on Form 10-K include, among other things, statements regarding:

- the initiation, timing, progress and results of current and future preclinical studies and clinical trials, and our research and development programs;
- the potential of isocitrate dehydrogenase 1 and 2, or IDH1 and IDH2, respectively, mutations, pyruvate kinase-R, or PKR, 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, mitapivat, AG-270 and AG-636;
- our plans to develop and commercialize our product candidates, including our ability to successfully commercialize TIBSOVO® and successfully commercialize IDHIFA® with our partner Celgene Corporation, or Celgene, a wholly-owned subsidiary of Bristol-Myers Squibb Company, or BMS;
- 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, for TIBSOVO® for previously treated IDH1 mutant-positive cholangiocarcinoma that we expect to submit to the U.S. Food and Drug Administration, or FDA, by the end of 2020;
- our strategic vision for 2025;
- the implementation of our business model and strategic plans for our business, product candidates and technology;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the rate and degree of market acceptance and clinical utility of our products;
- our competitive position;
- our intellectual property position;
- developments and projections relating to our competitors and our industry; and
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in this Annual Report on Form 10-K, particularly in the "Risk Factors" section, that could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we

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 creating differentiated, small molecule medicines for patients in the areas of hematologic malignancies, solid tumors and rare genetic diseases, or RGDs. To address these focus areas, 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.

Our wholly-owned product, TIBSOVO® (ivosidenib) is an oral targeted inhibitor of the mutated isocitrate dehydrogenase 1, or IDH1 enzyme. TIBSOVO® is the first and only U.S. Food and Drug Administration, or FDA-approved therapy for the treatment of adult patients with (i) relapsed or refractory acute myeloid leukemia, or R/R AML, with a susceptible IDH1 mutation as detected by an FDA-approved test (approved by the FDA in July 2018) and (ii) newly diagnosed AML with a susceptible IDH1 mutation as detected by an FDA-approved test who are at least 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy (approved by the FDA in May 2019). In December 2018, we submitted an Marketing Authorization Application, or MAA, to the European Medicines Agency, or EMA, for TIBSOVO® for the treatment of adult patients with R/R AML with an IDH1 mutation. In addition, we are currently evaluating ivosidenib in the clinical trials described below.

Our other marketed product is IDHIFA® (enasidenib), an oral targeted inhibitor of the mutated isocitrate dehydrogenase 2, or IDH2 enzyme and the first and only FDA-approved therapy for patients with R/R AML and an IDH2 mutation. 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. 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. In June 2018, Celgene submitted an MAA to the EMA for IDHIFA® for IDH2 mutant-positive AML which it subsequently withdrew in December 2019. 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-270, and AG-636.

Vorasidenib is an orally available, selective brain-penetrant pan-IDH mutant inhibitor. We are developing vorasidenib for the treatment of IDH mutant-positive low grade glioma and are currently evaluating vorasidenib in the clinical trials described below.

AG-270 is an orally available selective potent inhibitor of methionine adenosyltransferase 2a, or MAT2A. We are currently evaluating AG-270 in a phase 1 dose-escalation and expansion trial in multiple tumor types carrying a methylthioadenosine phosphorylase, or MTAP, deletion, described below.

AG-636 is an inhibitor of the metabolic enzyme dihydroorotate dehydrogenase, or DHODH. We are currently evaluating AG-636 in the phase 1 dose-escalation trial in lymphoma described below.

The lead product candidate in our RGD portfolio, mitapivat, is an activator of both wild-type and mutant pyruvate kinase-R for the potential treatment of hemolytic anemias. We are currently evaluating mitapivat for the treatment of pyruvate kinase, or PK, deficiency, thalassemia and sickle cell disease, or SCD, in the clinical trials described below.

In addition to the aforementioned development programs, we are seeking to advance a number of early-stage discovery programs in our focus areas of malignant hematology, solid tumors and RGDs based on our scientific leadership in the field of cellular metabolism and adjacent areas of biology.

Our approach to drug discovery involves collaboration across our core capabilities in bioinformatics, functional genomics, proteomics and metabolomics. We leverage these capabilities to identify under-researched targets, validate these targets using genetic and chemical approaches, and advance them rapidly into and through drug discovery. We believe that we have established state-of-the-art capabilities to study and drug metabolic targets including our ability to measure the activities of numerous metabolites in cells or tissues in a high throughput fashion, and measure metabolic fluxes. This refers to the analysis of how metabolites, which are intermediates or small molecule products of metabolism, accumulate or diminish as they are created or chemically altered by multiple networks of metabolic enzymes. Through our historic efforts to drug metabolic enzymes we have established strong capabilities in the enzymology and structural biology of metabolic enzymes, facilitating our drug discovery efforts.

We focus on the identification, validation, and drugging of targets with compelling patient selection biomarkers and robust pharmacodynamic readouts, thus increasing the potential for establishing proof of concept early in clinical development, along with the potential for accelerated approval.

Our Strategy and Long Term Goals

We aim to build a sustainable, multi-product company, based on our expertise in cellular metabolism and adjacent biology that creates differentiated, small molecule medicines for patients in the areas of malignant hematology, solid tumors and RGDs. Key elements of our strategy include:

- Building a preeminent independent biopharmaceutical company by aggressively pursuing the discovery, development and commercialization of novel medicines to transform the lives of patients with hematological malignancies, solid tumors and RGDs.
- Maintaining our focus on bio-marker driven drug discovery and development for defined patient subsets with high unmet need.
- Collaborating closely with the FDA and other regulatory bodies to aggressively pursue early registration potential for our product candidates.

As part of our long term strategy, we have developed and articulated a strategic vision that delineates our view for growth over the next six years, which we call "Agios 2025." Under this plan, by the end of 2025, our goal is to have four marketed medicines discovered and developed by us, with regulatory approvals in at least eight indications spanning hematologic malignancies, solid tumors and RGDs; to have at least six molecules in clinical development fueled by our internal research discovery engine; and to become cash flow positive.

Our Guiding Principles

We are driven by a disciplined focus on developing medicines that transform the lives of patients with hematological malignancies, solid tumors 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. Additionally, metabolites serve as key regulators of diverse aspects of cellular biology, and pharmacologic targeting of metabolism can therefore have disease-modifying effects in a wide variety of pathologies. 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 hematologic malignancies, solid tumors and RGDs.

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 altered. Carcinogens, or cancer causing agents, such as radiation, chemicals and hormones, can trigger changes to the genetic material of a cell, increasing the rate of new genetic alterations and thus promoting cancer. 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, 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. Historically, cancer drug development focused on design of cytotoxic drugs, which kill rapidly proliferating cells and are efficacious because of the unregulated cell growth that is characteristic of cancers. These drugs such as Cytoxan® and Adriamycin® have been effective in the treatment of some cancers, and remain in use today, but 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. In many cases, drug therapy entails the administration of several different drugs, known as combination chemotherapy.

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.

These newer therapies include: targeted therapies that inhibit the activity of specific enzymes that are mutated in specific subsets of cancers; drugs that stimulate the normal immune system to attack the cancer, also known as immuno-oncology; chimeric antigen receptor and T cell receptor technologies to genetically engineer T cells to recognize and kill cancer cells; antibody drug conjugates, for example 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, also known as epigenetics.

Emerging areas

Next generation targeted therapies. Targeted therapies, where the therapy is effective in a discrete subset of cancer patients who have specific cancer-causing mutations, have become an important component of cancer therapeutics. These drugs are designed to attack oncogenes, which are targets that are genetically altered in cancer cells, where the genetic alteration in the target causes uncontrolled growth of cancer cells. Examples of effective oncogene-targeted therapies include Herceptin®, Avastin® and Zelboraf®. Initial oncogene-targeted therapies were directed against mutant forms of cell surface receptors or enzymes involved in cellular signaling and cell growth control. Recently, the breadth of targets that have been drugged has been expanded to include other classes of mutant enzymes, including epigenetic enzymes, such as genetically altered forms of EZH2, and metabolic enzymes, such as genetically altered forms of IDH1 and IDH2.

As a class, oncogene-targeted therapies have proven effective in treating patients with the appropriate oncogene mutation, but only a fraction of cancer patients have mutations in these readily druggable targets. Targeted therapies for patients that do not currently benefit from oncogene-targeted therapies are a critical need, and we believe that synthetic lethal strategies are an important emerging approach to this problem. Synthetic lethal targets are targets that are more essential for the growth or survival of cancers with genetic alteration in a gene other than the target itself. In synthetic lethal approaches, the genetic alteration in the cancer creates a vulnerability to a second target. Poly (ADP-ribose) polymerase, or PARP, inhibitors in breast cancer gene, or BRCA-mutant cancers are an example of a synthetic lethal-targeted therapy. We believe that there are additional druggable targets that have synthetic lethal relationships with prevalent genetic alterations in cancer, and we continue to apply our research platform to identify and drug such targets, including MTAP-deleted cancers. Synthetic lethal targets are an important emerging class of precision medicines.

Next generation immuno-oncology therapies. In addition to unregulated growth pathways in the cells within a tumor, the growth and survival of the tumor also requires that the tumor is not recognized and attacked by the patient's immune system. Tumors employ a variety of strategies to avoid detection and killing by the immune system, and therapies that interfere with these strategies have recently been shown to be effective in multiple types of cancer. These therapies, such as Keytruda®, Opdivo® and Yervoy®, known as 'immune checkpoint' therapies, block the inactivation of endogenous T cells and allow them to attack the tumor. While highly effective in some patients, these therapies work in a minority of all cancers. A critical emerging area is the discovery of next-generation immuno-oncology therapies that, alone or in combination, will enhance immune-mediated killing of tumors. There is increasing evidence that there are additional immune checkpoints that have not yet been discovered or have not yet been therapeutically targeted. This includes evidence that specific metabolites can act locally in the tumor microenvironment as immuno-suppressants. We are leveraging our capabilities in bioinformatics, functional genomics, proteomics and metabolomics to identify, validate and drug novel immuno-oncology targets in metabolism and adjacent biology areas, and our efforts in this 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

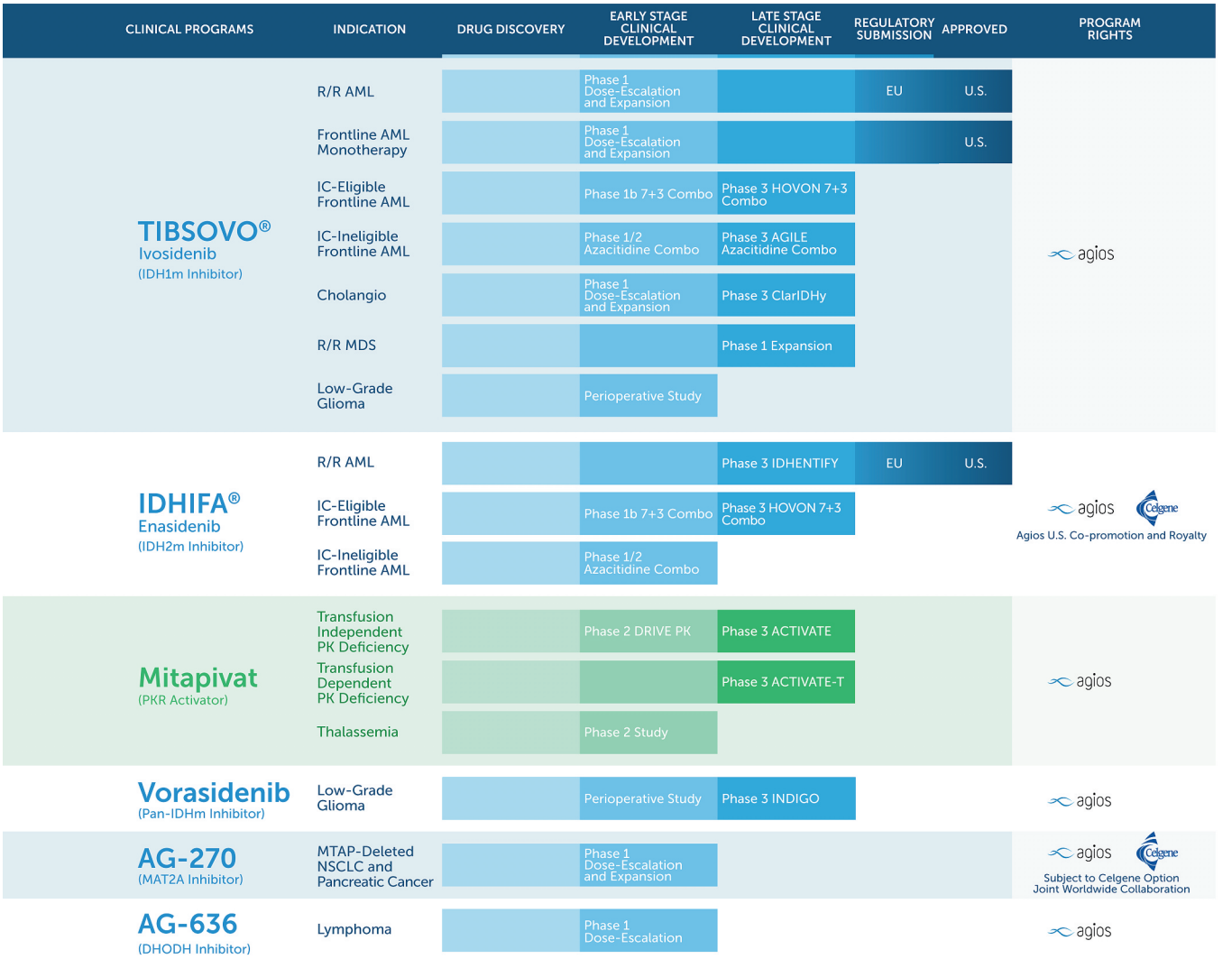
We will generally progress our drug candidates forward into phase 1 clinical trials if we have the ability to select patients who are most likely to respond to a given therapy based on biomarkers, for example, genetic or metabolic markers. To increase the probability of discovering and developing such precision medicines, we utilize translational science approaches throughout the research process, and we typically begin our efforts to identify novel targets by first specifying a biomarker-identifiable subset of disease with a high unmet need, and then conducting target identification and validation studies to identify targets that will be particularly well suited to that biomarker-identifiable population. In other words, we begin our research with specific, defined subsets of patients in mind.

While many factors are considered critical to maximize the probability of technical success in the drug development process, perhaps none is more important than identifying highly specific and selective molecules aimed at the best possible targets for therapy coupled with the patients most likely to respond to that therapy. Our goal is to develop increasing confidence in the target and the patient population prior to entering human clinical trials, and then initiate those first human trials in a patient population that has been selected based on target dependence using a genetic marker and/or biomarker. This approach, known as personalized or precision medicine, is used in the industry to lead to the potential for clear proof of concept in early human trials, along with the potential for accelerated approval.

Our Development Programs

We believe that leveraging our core capabilities in cellular metabolism combined with a precision medicine approach has significantly enhanced our ability to build a research and development engine that is focused in the therapeutic areas of malignant hematology, solid tumors 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 establishing early clinical proof of concept and accelerated approval paths.

The following summarizes our products and most advanced product candidates as of February 1, 2020, each of which is described in further detail below:



Targeting Mutated IDH for the Treatment of Cancer

The IDH protein is a critical enzyme in the citric acid cycle, also known as the tricarboxylic acid cycle or Krebs cycle. The Krebs cycle is centrally important to many biochemical pathways and is one of the earliest established components of cellular metabolism. The Krebs cycle converts an essential cellular metabolite called isocitrate into another metabolite, alpha-ketoglutarate (a-ketoglutarate), both of which are critically important for cellular function and the creation of energy. In 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 also 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 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, commonly used to treat

cancer, which lead to cell death. Our goal is to establish our IDH mutation inhibitors as a cornerstone of AML therapy spanning all treatment lines, and to leverage our understanding of IDH mutation inhibition to develop our IDH mutation inhibitors to treat solid tumors such as low grade glioma and cholangiocarcinoma.

To date, IDH1 and IDH2 mutations have been found to be prevalent in a broad range of advanced hematologic malignancies and solid tumors. The following table summarizes 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%
	Myelodysplastic Syndromes (MDS) / Myeloproliferative neoplasms (MPN)	~3%
IDH2	AML	~9-13%

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

Ivosidenib (mutant IDH1 inhibitor)

We are developing ivosidenib for the treatment of IDH1 mutant-positive cancers. Ivosidenib is an orally available, selective, potent inhibitor of the mutated IDH1 protein, making it a highly targeted therapy 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, MDS, cholangiocarcinoma and low grade 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. In May 2019, the FDA approved our sNDA to update the U.S. Prescribing Information for TIBSOVO® to include patients with newly diagnosed AML with a susceptible IDH1 mutation as detected by an FDA-approved test who are at least 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy. The FDA granted orphan drug designation for ivosidenib for the treatment of cholangiocarcinoma, granted Breakthrough Therapy designation for ivosidenib in combination with azacitidine for the treatment of newly diagnosed AML with an IDH1 mutation in adult patients who are at least 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy, and granted Breakthrough Therapy designation for ivosidenib for the treatment of adult patients with relapsed or refractory MDS with a susceptible IDH1 mutation as detected by an FDA-approved test.

We continue to evaluate ivosidenib in the following clinical trials:

Hematologic Malignancies

- A phase 1b, multicenter, international, open-label clinical trial, to evaluate 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. This trial has completed enrollment.
- A phase 1/2 frontline combination clinical trial, conducted by Celgene, of either ivosidenib or enasidenib in combination with VIDAZA® (azacitidine) in newly diagnosed AML patients not eligible for intensive chemotherapy. The trial has completed enrollment.
- 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.
- HO150/AMLSG29, an intergroup sponsored, global, registration-enabling phase 3 trial, supported in collaboration with Celgene, combining ivosidenib or enasidenib with standard induction and consolidation chemotherapy in frontline AML patients with an IDH1 or IDH2 mutation. The trial is currently enrolling patients.

- A phase 1 multicenter, open-label, dose-escalation and expansion clinical trial, designed to assess its safety, clinical activity and tolerability as a single agent in patients with advanced hematologic malignancies with an IDH1 mutation. The trial recently reopened enrollment of its relapsed or refractory MDS arm, for which we expect to complete enrollment in 2020.

Solid Tumors

- 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. The trial has completed enrollment.
- 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 primary endpoint of the trial was met and we expect to file an sNDA with the FDA for TIBSOVO® in cholangiocarcinoma by year-end 2020.

Enasidenib (mutant IDH2 inhibitor)

Celgene, pursuant to the 2010 Agreement, discussed below, is developing enasidenib for the treatment of IDH2 mutant-positive hematologic malignancies. 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, which it subsequently withdrew in December 2019.

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, 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 royalties at tiered low-double digit to mid-teen percentage rates 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 has completed enrollment.

Vorasidenib: brain penetrant pan-IDH program

We are developing vorasidenib for the treatment of IDH mutant-positive low grade glioma. Vorasidenib is an orally available, selective, brain-penetrant, pan-IDH mutant inhibitor. In connection with the termination of the AG-881 Agreements discussed below, Celgene is eligible to receive royalties from us at a low single-digit percentage rate on worldwide net sales of products containing vorasidenib.

We continue to evaluate vorasidenib in the following clinical trials:

- A phase 1 multi-center, open-label clinical trial of vorasidenib in patients with advanced IDH1 or IDH2 mutant-positive solid tumors, including glioma. The trial has completed enrollment.
- A perioperative study with ivosidenib and vorasidenib in low grade glioma to further investigate their effects on brain tumor tissue. The trial has completed enrollment.
- INDIGO, a registration-enabling phase 3 clinical trial of vorasidenib in low-grade (grade 2) glioma with an IDH1 or IDH 2 mutation. The trial is enrolling patients.

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 has several tissue-specific isoforms (PKR, PKL, PKM1 and PKM2). PKR is the isoform of pyruvate kinase that is present in red blood cells, or RBCs. Mutations in PKR cause defects in RBC 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, we believe that activation of mutant forms of PKR can restore glycolytic pathway activity and increase RBC health in patients with PK deficiency, and

activation of wild-type (non-mutated) PKR can serve as an effective compensatory mechanism in hemolytic anemias such as thalassemia and SCD.

PK Deficiency

PK deficiency is a rare genetic disorder and disease understanding is still evolving. We estimate that the prevalence of PK deficiency is between approximately 3,000 and 8,000 individuals in the United States and European Union, and we believe that the disease is likely under-diagnosed. PK deficiency leads to a shortened life span for RBCs and is the most common form of non-spherocytic hemolytic anemia in humans.

There is no currently known 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 chronic hemolysis can lead to long-term complications and comorbidities, regardless of the degree of the anemia, often resulting in jaundice and lifelong conditions associated with chronic anemia and secondary complications. The precise mechanism for the hemolysis 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%). Current management strategies for PK deficiency, including blood transfusion and splenectomy, are associated with both short- and long-term risks. More than 300 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, called PEAK, for up to 500 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 hemolytic anemia.

Thalassemia

Thalassemia is a hereditary blood disorder in which mutations in the α- or β-globin chains of hemoglobin lead to globin chain precipitates and aggregates that disturb the RBC membrane and induce oxidative stress, leading to decreased survival of RBC precursors, ineffective erythropoiesis, hemolysis of mature RBCs, and anemia. We estimate that the prevalence of thalassemia is between 18,000 and 23,000 individuals in the United States and European Union. In addition to anemia, patients with thalassemia can experience enlarged spleen, bone deformities, iron overload, fatigue, and infection. Current treatment strategies for thalassemia include blood transfusion and bone marrow transplantation, as well as recently improved therapies such as Reblozyl® for the treatment of beta thalassemia. We believe that the activation of wild-type PKR may increase ATP production and improve red cell fitness and survival of thalassemic RBCs, by increasing the clearance globin chain aggregates through ATP-dependent proteolytic mechanisms. In December 2019, we announced preliminary clinical data from our ongoing phase 2 trial of mitapivat in patients with non-transfusion-dependent thalassemia demonstrating proof of concept that activation of wild-type PKR has the potential to convey clinical benefit in thalassemia by increasing hemoglobin levels and reducing hemolysis in trial subjects.

Sickle Cell Disease

SCD is an inherited blood disorder caused by mutations in hemoglobin that enable the hemoglobin to form long polymeric chains under certain conditions such as low oxygenation, or deoxygenation. Polymerization of this irregular hemoglobin results in RBCs taking on a sickle shape, causing them to aggregate and obstruct small blood vessels, restricting blood flow to organs resulting in pain, cell death and organ damage. We estimate that the prevalence of SCD is between 120,000 and 135,000 individuals in the United States and EU. RBC deoxygenation is modulated by several factors, including the levels of 2,3-DPG, which is found to be elevated in sickle cell patient RBCs. Current treatment strategies focus on managing and preventing acute RBC sickling, and include hydroxyurea, L-glutamine and blood transfusions, as well as recently approved therapies such as Adakveo® and Oxbryta®. We believe that activation of wild-type PKR in patients with SCD may reduce hemoglobin polymerization and the sickling process by at least two mechanisms. Reducing the level of 2,3-DPG in RBCs would increase the oxygenation state of hemoglobin to reduce sickling, while increasing the levels of ATP may improve RBC hydration status which would also inhibit the sickling process.

Mitapivat: PK activator

We are developing mitapivat for the treatment of PK deficiency and other hemolytic anemias such as thalassemia and SCD. Mitapivat is an orally available small molecule and a potent activator of the wild-type and mutated PKR enzymes. To date, we

have demonstrated in clinical trials that treatment with mitapivat can lead to durable sustained increases in hemoglobin in patients with amenable mutations in the PKR gene, and observed early signs of improvements in hemoglobin in thalassemia patients who have wild-type PKR.

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 and fast track designations for mitapivat for the treatment of patients with PK deficiency.

We are evaluating mitapivat in the following clinical trials:

- 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. This trial has completed enrollment.
- ACTIVATE-T, a single arm, global, pivotal trial of mitapivat in up to 40 regularly-transfused patients with PK deficiency. The trial has completed enrollment.
- 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 trial has closed enrollment.
- A phase 2, open-label safety and efficacy clinical trial of mitapivat in approximately 20 adult patients with non-transfusion-dependent thalassemia. The trial is currently enrolling patients.
- In addition, in collaboration with the National Institutes of Health, or NIH, we are evaluating mitapivat in patients with SCD pursuant to a cooperative research and development agreement.

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. We have discovered small molecule inhibitors of MAT2A, including AG-270, that reduce SAM production and cause MTAP-null antiproliferative effects in cancer cell lines in vitro and in MTAP-deleted tumor models in vivo. MTAP deletion is readily detected by a genomic or immunohistochemistry test, thus allowing the selection of patients predicted to be sensitive to the therapy.

In March 2017, we announced that Celgene designated AG-270 as a development candidate under our 2016 research agreement with Celgene, or the 2016 Agreement. Pursuant to the 2016 Agreement, Celgene paid us an $8.0 million designation fee upon its designation of AG-270 as a development candidate. Exploratory research, drug discovery and early development of AG-270 is led by us, and Celgene will have an opt-in right on AG-270 up through phase 1 dose escalation for at least a $30.0 million fee. In October 2019, we formally submitted the opt-in package to Celgene and they have up to 150 days to make a decision. Should Celgene opt-in, we and Celgene would share 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.

We are evaluating AG-270 in a phase 1 trial in multiple tumor types carrying an MTAP deletion. The first part of the trial, which is complete, is a single agent dose-escalation phase in which cohorts of patients received ascending doses of AG-270 to determine the pharmacokinetics, pharmacodynamics and optimal dose, and schedule. The next phase of development, which was initiated in September 2019, is evaluating AG-270 in combination with taxanes in two areas of high unmet needs. One arm of the study will test AG-270 in combination with docetaxel in MTAP-deleted non-small cell lung cancer and the other arm will test AG-270 in combination with nab-paclitaxel and gemcitabine in MTAP-deleted pancreatic ductal adenocarcinoma. Both combination arms have initiated and are enrolling patients.

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

We have discovered a lineage-specific dependence on DHODH in hematologic malignancies, particularly AML and diffuse large B-cell lymphoma. DHODH catalyzes a critical step in the biosynthesis of pyridimidines, which are critical for the production of RNA and DNA. We believe that DHODH inhibition will be differentiated from standard-of-care therapies, both by exhibiting activity in cancers that are resistant to standard-of-care chemotherapeutics and through a mechanism of anti-tumor effect that combines cell growth arrest and cellular differentiation.

We are evaluating AG-636, an inhibitor of DHODH, licensed to us from Aurigene Discovery Technologies Limited in a phase 1 dose-escalation trial in subjects with advanced lymphomas. This trial is currently enrolling patients.

Collaborations with Celgene

In November 2019, the acquisition of Celgene was completed by BMS, and Celgene became a wholly-owned subsidiary. We will continue to refer to our collaboration agreements with Celgene throughout this Form 10-K as being with Celgene Corporation.

2016 Agreement

In May 2016, we entered into the 2016 Agreement focused on metabolic immuno-oncology, 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 having the right to be the lead party for the first such program, and each party will have a 50% profit or loss share. The lead party for the United States will book commercial sales of licensed products, if any, in the United States, and Celgene will book commercial sales of licensed products, if any, outside of the United States.

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

Financial terms. Under the terms of the 2016 Agreement, we received an initial upfront payment in the amount of $200.0 million. The 2016 Agreement provides specified rights to extend the research term for up to two, or in specified cases, up

to four, additional years by paying a $40.0 million per-year extension fee. Celgene will pay an $8.0 million designation fee for each program that Celgene designates for further development and for each continuation program. During the year ended December 31, 2017, we received $8.0 million from Celgene upon the designation of AG-270, our MAT2A inhibitor, as a development candidate. For each program as to which Celgene exercises its option to develop and commercialize, subject to antitrust clearance, Celgene will pay an option exercise fee of at least $30.0 million for any designated development program and at least $35.0 million for any continuation programs. In certain cases, Celgene may exercise its option to develop and commercialize two early-stage I&I programs, prior to Celgene designating the program for further development, by paying an option exercise fee of $10.0 million per program.

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). Under specified circumstances, either party may terminate the 2016 Agreement either in its entirety or on a program-by-program basis. Either party also has the right to terminate the co-development and co-commercialization agreement or license agreement if the other party or any of its affiliates challenges the validity, scope or enforceability of or otherwise opposes, any patent included within the intellectual property rights licensed to the other party under such agreement.

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

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

Ivosidenib Letter Agreement

On May 17, 2016, we entered into a letter agreement with Celgene regarding ivosidenib, or the Ivosidenib Letter Agreement. Under the Ivosidenib Letter Agreement, the parties agreed to terminate the 2010 Agreement, effective as of August 15, 2016, as to the program directed to the IDH1 target, for which ivosidenib is the lead development candidate. Under the 2010 Agreement, Celgene had held development and commercialization rights to the IDH1 program outside of the United States, and we held such rights inside the United States. As a result of the Ivosidenib Letter Agreement, we obtained global rights to ivosidenib and

the IDH1 program. Neither party will have any further financial obligation, including royalties or milestone payments, to the other concerning ivosidenib or the IDH1 program. Under the terms of the Ivosidenib Letter Agreement, the parties also agreed to conduct specified transitional activities in connection with the termination. In addition, pursuant to the Ivosidenib Letter Agreement, the parties are released from their exclusivity obligations under the 2010 Agreement with respect to the IDH1 program. The Ivosidenib Letter Agreement does not affect the AG-881 Agreements, which were directed to both the IDH1 target and the IDH2 target, and were subsequently terminated in September 2018 as discussed below.

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 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. 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 is eligible to receive royalties from us at a low single-digit percentage rate on worldwide net sales of products containing vorasidenib and (b) we and Celgene agreed to split certain agreed-upon worldwide development costs for vorasidenib until December 31, 2018. In addition, for a specified period and subject to specified exceptions, Celgene and its affiliates are prohibited from developing, manufacturing or commercializing any product that inhibits IDH1 at specified levels of binding for any indication and we are prohibited from developing, manufacturing or commercializing vorasidenib 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 are eligible to 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, 2019, we earned $10.5 million in royalty revenue under the 2010 Agreement.

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

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 added 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; we serve as co-sponsor with CStone for local studies of ivosidenib in AML. 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 mainland 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 mainland 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 who have an IDH1 mutation.

Pursuant to the CStone Agreement, we have entered into a clinical supply agreement and pharmacovigilance agreement with CStone, and will enter into further ancillary agreements, including commercial supply agreements.

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), 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, 2020 we owned or licensed approximately issued 31 U.S. patents, 316 issued foreign patents, 37 pending U.S. patent applications, 460 pending foreign patent applications, and 13 pending Patent Cooperation Treaty, or PCT, patent applications, directed to our key product candidates, related compounds and potential backup compounds. The foreign issued patents and patent applications are in a number of jurisdictions, including Argentina, Australia, Austria, Belgium, Brazil, Canada, China, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Japan, Lithuania, Mexico, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom.

The intellectual property portfolios for our most advanced programs as of February 1, 2020 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 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, 2020, we owned approximately 21 issued U.S. patents, 152 issued foreign patents, 24 pending U.S. patent applications, 327 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 2039. 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 and AG-946, as well as analogs thereof, various solid state forms of these compounds, as well as methods of use for these novel compounds. As of February 1, 2020, we owned approximately 5 issued U.S. patents, 116 issued foreign patents, 6 pending U.S. patent applications, 44 pending foreign patent applications in a number of jurisdictions, and 3 pending PCT patent applications, directed to our PK activator program, including our product candidates. 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 related compound families including potential backup compounds, as well as methods of use for these novel compounds and diagnostic methods for detecting MTAP deletions. As of February 1, 2020, we owned approximately 1 issued U.S. patent, 4 pending U.S. patent applications, 1 foreign issued patent, 46 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 2036 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 and formulations of AG-636 and methods of use for these forms of AG-636, other methods of use for AG-636 and methods of use and diagnostic methods relating to AG-636 and other DHODH inhibitors. As of February 1, 2020, we exclusively licensed or independently filed approximately 4 issued U.S. patents, 47 issued foreign patents, 3 pending U.S. patent applications, 43 pending foreign patent applications, and 2 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 be issued or that we will benefit from any patent term extension or favorable adjustment to the term of any of our patents.

As with other biotechnology and pharmaceutical companies, our ability to maintain and solidify our proprietary and intellectual property position for our product candidates and technologies will depend on our success in obtaining effective patent claims and enforcing those claims if granted. However, patent applications that we may file or license from third parties may not result in the issuance of patents. We also cannot predict the breadth of claims that may be allowed or enforced in our patents. Any issued patents that we may receive in the future may be challenged, invalidated or circumvented. For example, we cannot be certain of the priority of inventions covered by pending third-party patent applications. If third parties prepare and file patent applications in the United States that also claim technology or therapeutics to which we have rights, we may have to participate in interference proceedings with 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 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 areas of pharmaceutical, biotechnology and other related markets that address hematologic malignancies, solid tumors and RGDs. There are other companies working to develop therapies in the fields of hematologic malignancies, solid tumors and RGDs. These companies include divisions of large pharmaceutical companies and biotechnology companies of various sizes.

Malignant Hematology and Solid Tumors. In the fields of malignant hematology and solid tumors, our principal competitors include AbbVie Inc., ASLAN Pharmaceuticals Limited; AstraZeneca Plc.; Astellas Pharma Inc.; Bayer AG; BeiGene Ltd.; BMS; 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. The most common methods of treating patients with hematologic malignancies and solid tumors are surgery, radiation and drug therapy, including chemotherapy, hormone therapy and targeted drug therapy, and there are a variety of available drug therapies marketed for these cancer types. 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. Recently approved treatments for solid tumors include Keytruda® from Merck, Rozlytrek® from Roche and Vitrakvi® from Bayer (in collaboration with Loxo Oncology, Inc.), and 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 hematologic malignancies and solid tumors. 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; ASLAN, Bayer, Clear Creek Bio, and PTC Therapeutics, Inc. are conducting clinical trials of their DHODH inhibitors in hematologic malignancies; and IDEAYA Biosciences, Inc is developing a MAT2A inhibitor for the treatment of MTAP-deleted solid tumors. 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.; Forma; Novartis; Pfizer; Global Blood Therapeutics; 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 therapies available for treating patients with RGDs. For example, recently-approved treatments for thalassemia, sickle cell disease, and phenylketonuria include Reblozyl® from Acceleron (in collaboration with BMS); Lentiglobin® from bluebird; Adakveo® from Novartis; Oxbryta® from Global Blood; and Kuvan® and Palynziq® from BioMarin. 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. For example, Forma is conducting phase 1 clinical trial of their PKR activator, FT-4202, in patients with SCD. 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 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, 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. Due to the volatility of the raw material supply network globally, we have gained regulatory approval for redundant supply of raw materials, and have an ongoing program to ensure this risk mitigation remains effective. We do not currently have arrangements in place for redundant supply for bulk drug substance and drug product, but maintain a broad safety stock program. 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, 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.

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 investigational new drug application, or 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 risk evaluation and mitigation strategies, or 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.

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 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 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 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 NDA. 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 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.

On December 13, 2016, the 21st Century Cures Act established (and the 2017 FDA Reauthorization Act later amended) a requirement that sponsors of one or more investigational drugs for the treatment of a serious disease or condition make publicly available their policy for evaluating and responding to requests for expanded access for individual patients. Although these requirements were rolled out over time, they have now come into full effect. This provision requires drug and biologic companies to make publicly available their policies for expanded access for individual patient access to products intended for serious diseases. Sponsors are required to make such policies publicly available upon the earlier of initiation of a Phase 2 or Phase 3 study, or 15 days after the drug or biologic receives designation as a breakthrough therapy, fast track product, or regenerative medicine advanced therapy.

In addition, on May 30, 2018, the Right to Try Act was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase I clinical trial and are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act, but the manufacturer must develop an internal policy and respond to patient requests according to that policy.

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. 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 2020 is $2,943,956 for an application requiring clinical data. The sponsor of an approved NDA is also subject to an annual program fee, which for fiscal year 2020 is $325,424. 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 NME.

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 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 IMM 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 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, or OCE, the FDA has established two pilot programs allowing for real-time review of sNDAs 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 sNDA. 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 determine whether a sNDA 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. SNDAs 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 the 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

Based on its 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 the approved 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. Accordingly, the sponsor 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 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, 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 DOJ, 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 DSCSA, 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 DSCSA 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 "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 an 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, or NCE. For the purposes of this provision an 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.

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 an NCE, 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, the FDA will meet early in the development process to discuss pediatric study plans with sponsors, and the 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 the FDA's receipt of the study plan.

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in the Food and Drug Administration Safety and Innovation Act, or 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 the 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. With regard to patents, the six-month pediatric exclusivity period will not attach to any patents for which a generic (ANDA or 505(b)(2) NDA) applicant submitted a paragraph IV patent certification, unless the NDA sponsor or patent owner first obtains a court determination that the patent is valid and infringed by a proposed generic product.

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may designate a drug product as an "orphan drug" if it is intended to treat a rare disease or condition, generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a 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 when a clinical investigation involving human beings has 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 the FDA determines that a companion diagnostic device is essential to the safe and effective use of a novel therapeutic product or indication, the FDA generally will not approve the therapeutic product or new therapeutic product indication if the companion diagnostic device is not approved or cleared for that indication. Approval or clearance of the companion diagnostic device will ensure that the device has been adequately evaluated and has adequate performance characteristics in the intended population. The review of *in vitro* companion diagnostics in conjunction with the review of our therapeutic treatments for cancer will, therefore, likely involve coordination of review by the FDA's Center for Drug Evaluation and Research and the FDA's Center for Devices and Radiological Health Office of In Vitro Diagnostics Device Evaluation and Safety.

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

The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, can take several years or longer. It involves a rigorous premarket review during which the applicant must prepare and provide the FDA with reasonable assurance of the device's safety and effectiveness, and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications are subject to an application fee, which exceeds $250,000 for most PMAs. In addition, PMAs for certain devices must generally include the results from extensive preclinical and adequate and well-controlled clinical trials to establish the safety and effectiveness of the device for each indication for which FDA approval is sought. In particular, for a diagnostic, a PMA application typically requires data regarding analytical and clinical validation studies. As part of the PMA review, the FDA will typically inspect the manufacturer's facilities for compliance with the Quality System Regulation, 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 the data submitted in an amendment to the PMA. If the FDA concludes that the applicable criteria have been met, the FDA will issue a PMA for the approved indications, which can be more limited than those originally sought by the applicant. The PMA can include post-approval conditions that the FDA believes necessary to ensure the safety and effectiveness of the device, including, among other things, restrictions on labeling, promotion, sale and distribution. Once granted, PMA approval may be withdrawn by the FDA if 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.

- 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 ACA, 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 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 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, 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 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 liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs, and revising the definition of "average manufacturer price," or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices;
- addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;
- expanded the types of entities eligible for the 340B drug discount program;
- established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 50% (and 70% starting January 1, 2019) point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers up to 2% per fiscal year, which went into effect in April 2013 and, due to subsequent legislative amendments, will remain in effect through 2027 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Since enactment of the ACA, there have been numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017, or TCJA, which was signed by the President on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, which became effective in 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. Further, the Bipartisan Budget Act of 2018, among other things, amends the ACA, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole".

On December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and inseverable feature of the ACA, and therefore because the mandate was repealed as part of the TCJA, the remaining provisions of the ACA are invalid as well. The Trump Administration and CMS have both stated that the ruling will have no immediate effect, and on December 30, 2018 the same judge issued an order staying the judgment pending appeal. The Trump Administration thereafter represented to the Court of Appeals considering this judgment that it does not oppose the lower court's ruling. On July 10, 2019, the Court of Appeals for the Fifth Circuit heard oral argument in this case. In

those arguments, the Trump Administration argued in support of upholding the lower court decision. On December 18, 2019, that court affirmed the lower court's ruling that the individual mandate portion of the ACA is unconstitutional and remanded the case to the district court for reconsideration of the severability question and additional analysis of the provisions of the ACA. On January 21, 2020, the U.S. Supreme Court declined to review this decision on an expedited basis. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

Since January 2017, President Trump has signed two Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. The second Executive Order terminates the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. In addition, the CMS has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. Further, on June 14, 2018, the U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in ACA risk corridor payments to third-party payors who argued were owed to them. The effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business, are not yet known.

Further, there have been several recent U.S. congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, the Trump administration's budget proposal for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, allow some states to negotiate drug prices under Medicaid, and eliminate cost sharing for generic drugs for low-income patients. While any proposed measures will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. For example, on December 23, 2019, the Trump Administration published a proposed rule that, if finalized, would allow states or certain other non-federal government entities to submit importation program proposals to the FDA for review and approval. Applicants would be required to demonstrate their importation plans pose no additional risk to public health and safety and will result in significant cost savings for consumers. At the same time, the FDA issued draft guidance that would allow manufacturers to import their own FDA-approved drugs that are authorized for sale in other countries (multi-market approved products).

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing.

Review and Approval of Medicinal Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy, and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, an applicant will need to obtain the necessary approvals by the comparable non-U.S. regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. Specifically, the process governing approval of medicinal products in the EU generally follows the same lines as in the United States. It entails satisfactory completion of preclinical studies and adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication. It also requires the submission to the relevant competent authorities of an MAA and granting of a marketing authorization by these authorities before the product can be marketed and sold in the EU.

Clinical Trial Approval

The Clinical Trials Directive 2001/20/EC, the Directive 2005/28/EC on Good Clinical Practice, or GCP, and the related national implementing provisions of the individual EU Member States govern the system for the approval of clinical trials in the EU. Under this system, an applicant must obtain prior approval from the competent national authority of the EU Member

States in which the clinical trial is to be conducted. Furthermore, the applicant may only start a clinical trial at a specific study site after the competent ethics committee has issued a favorable opinion. The clinical trial application must be accompanied by, among other documents, an investigational medicinal product dossier (the Common Technical Document) with supporting information prescribed by Directive 2001/20/EC, Directive 2005/28/EC, where relevant the implementing national provisions of the individual EU Member States and further detailed in applicable guidance documents.

In April 2014, the Clinical Trial (Regulation, (EU)) No 536/2014 was adopted. The Clinical Trial Regulation was published on June 16, 2014 but is not expected to apply until 2020. The Clinical Trial Regulation will be directly applicable in all the EU Member States, repealing the current Clinical Trials Directive 2001/20/EC and replacing any national legislation that was put in place to implement the Directive. Conduct of all clinical trials performed in the EU will continue to be bound by currently applicable provisions until the new Clinical Trial Regulation becomes applicable. The extent to which on-going clinical trials will be governed by the Clinical Trial Regulation will depend on when the Clinical Trial Regulation becomes applicable and on the duration of the individual clinical trial. If a clinical trial continues for more than three years from the day on which the Clinical Trial Regulation becomes applicable the Clinical Trial Regulation at that time will begin to apply to the clinical trial.

The new Clinical Trial Regulation aims to simplify and streamline the approval of clinical trials in the EU. The main characteristics of the regulation include: a streamlined application procedure via a single entry point, the EU Portal and Database; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts. Part I is assessed by the appointed reporting Member State, whose assessment report is submitted for review by the sponsor and all other competent authorities of all EU Member States in which an application for authorization of a clinical trial has been submitted, or Concerned Member States. Part II is assessed separately by each Concerned Member State. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the Concerned Member State. However, overall related timelines will be defined by the Clinical Trial Regulation.

PRIME Designation in the EU

In March 2016, the EMA launched an initiative to facilitate development of product candidates in indications, often rare, for which few or no therapies currently exist. The priority medicines, or PRIME, scheme is intended to encourage drug development in areas of unmet medical need and provides accelerated assessment of products representing substantial innovation reviewed under the centralized procedure. Products from small- and medium-sized enterprises, or SMEs, may qualify for earlier entry into the PRIME scheme than larger companies. Many benefits accrue to sponsors of product candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other development program elements, and accelerated marketing authorization application assessment once a dossier has been submitted. Importantly, a dedicated Agency contact and rapporteur from the Committee for Human Medicinal Products, or CHMP, or Committee for Advanced Therapies, or CAT, are appointed early in the PRIME scheme facilitating increased understanding of the product at EMA's Committee level. A kick-off meeting initiates these relationships and includes a team of multidisciplinary experts at the EMA to provide guidance on the overall development and regulatory strategies.

Marketing Authorization

To obtain a marketing authorization for a product under EU regulatory systems, an applicant must submit an MAA either under a centralized procedure administered by the EMA, or one of the procedures administered by competent authorities in the EU Member States, decentralized procedure; national procedure; or mutual recognition procedure. A marketing authorization may be granted only to an applicant established in the EU. Regulation (EC) No 1901/2006 provides that prior to obtaining a marketing authorization in the EU, applicants have to demonstrate compliance with all measures included in an EMA-approved Paediatric Investigation Plan, or PIP, covering all subsets of the pediatric population, unless the EMA has granted: (1) a product-specific waiver; (2) a class waiver; or (3) a deferral for one or more of the measures included in the PIP.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid across the European Economic Area (i.e., the EU as well as Iceland, Liechtenstein and Norway). Pursuant to Regulation (EC) No 726/2004, the centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy medicinal products, or ATMPs, and products with a new active substance indicated for the treatment of certain diseases, including products for the treatment of cancer. For products with a new active substance indicated for the treatment of other diseases and products that are highly innovative or for which a centralized process is in the interest of patients, the centralized procedure may be optional. The centralized procedure may at the request of the applicant also be used in certain other cases. We anticipate that the centralized procedure will be mandatory for the product candidates we are developing.

Under the centralized procedure, the CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure in the

EU, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops, when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and from the viewpoint of therapeutic innovation. If the CHMP accepts such request, the time limit of 210 days will be reduced to 150 days, but it is possible that the CHMP can revert to the standard time limit for the centralized procedure if it considers that it is no longer appropriate to conduct an accelerated assessment. At the end of this period, the CHMP provides a scientific opinion on whether or not a marketing authorization should be granted in relation to a medicinal product. Within 15 calendar days of receipt of a final opinion from the CHMP, the European Commission must prepare a draft decision concerning an application for marketing authorization. This draft decision must take the opinion and any relevant provisions of EU law into account. Before arriving at a final decision on an application for centralized authorization of a medicinal product, the European Commission must consult the Standing Committee on Medicinal Products for Human Use, or Standing Committee. The Standing Committee is composed of representatives of the EU Member States and chaired by a non-voting European Commission representative. The European Parliament also has a related "droit de regard". The European Parliament's role is to ensure that the European Commission has not exceeded its powers in deciding to grant or refuse to grant a marketing authorization.

The European Commission may grant a so-called "marketing authorization under exceptional circumstances". Such authorization is intended for products for which the applicant can demonstrate that it is unable to provide comprehensive data on the safety and efficacy under normal conditions of use, because the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or in the present state of scientific knowledge, comprehensive information cannot be provided, or it would be contrary to generally accepted principles of medical ethics to collect such information. Consequently, marketing authorization under exceptional circumstances may be granted subject to certain specific obligations, which may include the following:

- the applicant must complete an identified program of studies within a time period specified by the competent authority, the results of which form the basis of a reassessment of the benefit/risk profile;
- the medicinal product in question may be supplied on medical prescription only and in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radiopharmaceutical, by an authorized person; and
- the package leaflet and any medical information must draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

A marketing authorization under exceptional circumstances is subject to annual review to reassess the risk-benefit balance in an annual reassessment procedure. Continuation of the authorization is linked to the annual reassessment, and a negative assessment could potentially result in the marketing authorization being suspended or revoked. The renewal of a marketing authorization of a medicinal product under exceptional circumstances, however, follows the same rules as a "normal" marketing authorization. Thus, a marketing authorization under exceptional circumstances is granted for an initial five years, after which the authorization will become valid indefinitely, unless the EMA decides that safety grounds merit one additional five-year renewal.

The European Commission may also grant a so-called "conditional marketing authorization" prior to obtaining the comprehensive clinical data required for an application for a full marketing authorization. Such conditional marketing authorizations may be granted for product candidates (including medicines designated as orphan medicinal products), if (i) the risk-benefit balance of the product candidate is positive; (ii) it is likely that the applicant will be in a position to provide the required comprehensive clinical trial data; (iii) the product fulfills an unmet medical need; and (iv) the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required. A conditional marketing authorization may contain specific obligations to be fulfilled by the marketing authorization holder, including obligations with respect to the completion of ongoing or new studies, and with respect to the collection of pharmacovigilance data. Conditional marketing authorizations are valid for one year, and may be renewed annually, if the risk-benefit balance remains positive, and after an assessment of the need for additional or modified conditions and/or specific obligations. The timelines for the centralized procedure described above also apply with respect to the review by the CHMP of applications for a conditional marketing authorization.

The EU medicines rules expressly permit the EU Member States to adopt national legislation prohibiting or restricting the sale, supply or use of any medicinal product containing, consisting of or derived from a specific type of human or animal cell, such as embryonic stem cells. While the products we have in development do not make use of embryonic stem cells, it is possible that the national laws in certain EU Member States may prohibit or restrict us from commercializing our products, even if they have been granted an EU marketing authorization.

Unlike the centralized authorization procedure, the decentralized marketing authorization procedure requires a separate application to, and leads to separate approval by, the competent authorities of each EU Member State in which the product is to

be marketed. This application is identical to the application that would be submitted to the EMA for authorization through the centralized procedure. The reference EU Member State prepares a draft assessment and drafts of the related materials within 120 days after receipt of a valid application. The resulting assessment report is submitted to the concerned EU Member States who, within 90 days of receipt, must decide whether to approve the assessment report and related materials. If a concerned EU Member State cannot approve the assessment report and related materials due to concerns relating to a potential serious risk to public health, disputed elements may be referred to the European Commission, whose decision is binding on all EU Member States.

The mutual recognition procedure similarly is based on the acceptance by the competent authorities of the EU Member States of the marketing authorization of a medicinal product by the competent authorities of other EU Member States. The holder of a national marketing authorization may submit an application to the competent authority of an EU Member State requesting that this authority recognize the marketing authorization delivered by the competent authority of another EU Member State.

Regulatory Data Protection in the EU

In the EU, innovative medicinal products approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Directive 2001/83/EC. Regulation (EC) No 726/2004 repeats this entitlement for medicinal products authorized in accordance with the centralized authorization procedure. Data exclusivity prevents applicants for authorization of generics of these innovative products from referencing the innovator's data to assess a generic (abridged) application for a period of eight years. During an additional two-year period of market exclusivity, a generic MAA can be submitted and authorized, and the innovator's data may be referenced, but no generic medicinal product can be placed on the EU market until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be an NCE so that the innovator gains the prescribed period of data exclusivity, another company nevertheless could also market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical, preclinical and clinical trials.

Periods of Authorization and Renewals

A marketing authorization has an initial validity for five years in principle. The marketing authorization may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance by the EMA or by the competent authority of the EU Member State. To this end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. The European Commission or the competent authorities of the EU Member States may decide, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year period of marketing authorization. Once subsequently definitively renewed, the marketing authorization shall be valid for an unlimited period. Any authorization which is not followed by the actual placing of the medicinal product on the EU market (in case of centralized procedure) or on the market of the authorizing EU Member State within three years after authorization ceases to be valid (the so-called sunset clause).

Pediatric Studies and Exclusivity

Prior to obtaining a marketing authorization in the EU, applicants must demonstrate compliance with all measures included in an EMA-approved PIP covering all subsets of the pediatric population, unless the EMA has granted a product-specific waiver, a class waiver, or a deferral for one or more of the measures included in the PIP. The respective requirements for all marketing authorization procedures are laid down in Regulation (EC) No 1901/2006, the so-called Pediatric Regulation. This requirement also applies when a company wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorized. The Pediatric Committee of the EMA, or PDCO, may grant deferrals for some medicines, allowing a company to delay development of the medicine for children until there is enough information to demonstrate its effectiveness and safety in adults. The PDCO may also grant waivers when development of a medicine for children is not needed or is not appropriate, such as for diseases that only affect the elderly population. Before an MAA can be filed or an existing marketing authorization can be amended, the EMA requests that companies comply with the agreed studies and measures listed in each relevant PIP. If an applicant obtains a marketing authorization in all EU Member States, or a marketing authorization granted in the centralized procedure by the European Commission, and the study results for the pediatric population are included in the product information, even when negative, the medicine is then eligible for an additional six month period of qualifying patent protection through extension of the term of the Supplementary Protection Certificate.

Orphan Drug Designation and Exclusivity

Regulation (EC) No. 141/2000, as implemented by Regulation (EC) No. 847/2000 provides that a drug can be designated as an orphan drug by the European Commission if its sponsor can establish that the product is intended for the diagnosis, prevention

or treatment of: (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the EU when the application is made; or (2) a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that the marketing of the drug in the EU would generate sufficient return to justify the necessary investment. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the EU or, if such method exists, the drug will be of significant benefit to those affected by that condition.

Once authorized, orphan medicinal products are entitled to 10 years of market exclusivity in all EU Member States and a range of other benefits during the development and regulatory review process, including scientific assistance for study protocols, authorization through the centralized marketing authorization procedure covering all member countries, and a reduction or elimination of registration and marketing authorization fees. However, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the 10-year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if this product is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if it can be demonstrated on the basis of available evidence that the original orphan medicinal product is sufficiently profitable not to justify maintenance of market exclusivity.

Regulatory Requirements after a Marketing Authorization has been Obtained

When an authorization for a medicinal product in the EU is obtained, the holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of medicinal products. These include:

- The EU's pharmacovigilance or safety reporting rules, which can impose post-authorization studies and additional monitoring obligations.
- The manufacturing of authorized medicinal products, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the applicable EU laws, regulations and guidance, including Directive 2001/83/EC, Directive 2003/94/EC, Regulation (EC) No 726/2004 and the European Commission Guidelines for Good Manufacturing Practice. These requirements include compliance with EU cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients, including the manufacture of active pharmaceutical ingredients outside of the EU with the intention to import the active pharmaceutical ingredients into the EU.
- The marketing and promotion of authorized drugs, including industry-sponsored continuing medical education and advertising directed toward the prescribers of drugs and/or the general public, are strictly regulated in the EU notably under Directive 2001/83EC, as amended, and EU Member State laws. Direct-to-consumer advertising of prescription medicines is prohibited across the EU.

General Data Protection Regulation

The collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the EU, including personal health data, is subject to the EU General Data Protection Regulation, or GDPR, which became effective on May 25, 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes rules on the transfer of personal data to countries outside the EU, including the United States, and permits data protection authorities to impose penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR will be a rigorous and time-intensive process that may increase the cost of doing business or require companies to change their business practices to ensure full compliance.

Brexit and the Regulatory Framework in the United Kingdom

On June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the EU, commonly referred to as Brexit. Following protracted negotiations, the United Kingdom left the EU on January 31, 2020. Under the withdrawal agreement, there is a transitional period until December 31, 2020 (extendable up to two years). Discussions between the United Kingdom and the EU have so far mainly focused on finalizing withdrawal issues and transition agreements but have been extremely difficult to date. To date, only an outline of a trade agreement has been reached. Much remains open but the Prime Minister has indicated that the United Kingdom will not seek to extend the transitional period beyond the end of 2020. If no trade agreement

has been reached before the end of the transitional period, there may be significant market and economic disruption. The Prime Minister has also indicated that the United Kingdom will not accept high regulatory alignment with the EU.

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

Pricing Decisions for Approved Products

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

Segment Reporting and Geographical Information

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

Revenue

The composition of our revenues for the years ended December 31, 2019, 2018, and 2017 consisted of the following:

	2019	2018	2017
Collaboration and royalty revenues - Celgene	42 %	72 %	100 %
Collaboration revenue - CStone	7 %	13 %	— %
Product revenue, net	51 %	15 %	— %

Our product sales to one specialty distributor, McKesson, and one specialty pharmacy, Biologics, each accounted for more than 10% of our consolidated revenues for the year ended December 31, 2019. No customers accounted for more than 10% of our consolidated revenues for year ended December 31, 2018. Refer to Note 10. *Product Revenue* and Note 11. *Collaboration and License Agreements* to the consolidated financial statements in this Annual Report on Form 10-K for additional information.

Our Scientific Advisors

Scientific Advisors

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

Name	Primary affiliation
Joan Brugge, Ph.D.	Harvard Medical School
Lewis C. Cantley, Ph.D.	The Cancer Center at Weill Cornell Medical College and New York-Presbyterian Hospital
Ralph Deberardinis, M.D., Ph.D.	Children's Medical Center Research Institute at University of Texas Southwestern
William G. Kaelin, Jr., M.D.	Dana-Farber Cancer Institute and Harvard Medical School
Tak W. Mak, Ph.D.	University of Toronto and the Campbell Family Institute for Breast Cancer Research
Pier Paolo Pandolfi, M.D., Ph.D.	Beth Israel Deaconess Medical Center
Charles Sawyers, M.D.	Memorial Sloan-Kettering Cancer Center
Shin-San Michael Su, Ph.D.	Decibel Therapeutics
Marc Tessier-Lavigne, Ph.D.	Stanford University
Craig B. Thompson, M.D.	Memorial Sloan-Kettering Cancer Center
Matthew Vander Heiden, M.D., Ph.D.	Koch Institute for Integrative Cancer Research at Massachusetts Institute of Technology

Employees

As of December 31, 2019, we had 536 full-time employees, including 158 employees with M.D. or Ph.D. degrees. Of these full-time employees, 368 employees are engaged in research and development activities. None of our employees are represented by a labor union or covered by a collective bargaining agreement. We consider our relationship with our employees to be good.

Our Corporate Information

We were incorporated under the laws of the State of Delaware in August 2007. Our executive offices are located at 88 Sidney Street, Cambridge, Massachusetts 02139, and our telephone number is (617) 649-8600. Our website address is www.agios.com. References to our website are inactive textual references only and the content of our website should not be deemed incorporated by reference into this Form 10-K.

Available Information

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

A copy of our Corporate Governance Guidelines, Code of Business Conduct and Ethics and the charters of the Audit Committee, Compensation Committee, and Nominating and Corporate Governance Committee are posted on our website, www.agios.com, under the heading "Corporate Governance" and are available in print to any person who requests copies by contacting us by calling (617) 649-8600 or by writing to Agios Pharmaceuticals, Inc., 88 Sidney Street, Cambridge, Massachusetts 02139.

Item 1A. Risk Factors

The following risk factors and other information included in this Annual Report on Form 10-K should be carefully considered. The risks and uncertainties described below are not the only risks and uncertainties we face. Additional risks and uncertainties not presently known to us or that we presently deem less significant may also impair our business operations. Please see page 1 of this Annual Report on Form 10-K for a discussion of some of the forward-looking statements that are qualified by these risk factors. If any of the following risks occur, our business, financial condition, results of operations and future growth prospects could be materially and adversely affected.

Risks Related to Our Financial Position and Need for Additional Capital

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

Since inception, we have incurred significant operating losses. Our net losses were $411.5 million, $346.0 million and $314.7 million for the years ended December 31, 2019, 2018 and 2017, respectively. As of December 31, 2019, we had an accumulated deficit of $1,516.1 million. To date, we have generated only modest revenue from sales of TIBSOVO® and royalties on sales of IDHIFA®. The FDA approved IDHIFA® for the treatment of adult patients with R/R AML and an IDH2 mutation, and approved TIBSOVO® for the treatment of adult patients with R/R AML with a susceptible IDH1 mutation and the treatment of adult patients with newly diagnosed AML with a susceptible IDH1 mutation who are at least 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy. We have not obtained marketing approval for any of our other product candidates, which are in preclinical or clinical development stages. We have financed our operations primarily through private placements of our preferred stock, our initial public offering and the concurrent private placement, our follow-on public offerings and our collaboration agreements with Celgene focused on cancer metabolism and metabolic immuno-oncology. We have devoted substantially all of our efforts to research and development. We expect to continue to incur significant expenses and net losses until such time we are able to report profitable results. The net losses we incur may fluctuate significantly from quarter to quarter. We anticipate that we will incur significant expenses if and as we:

- initiate and continue clinical trials for our products and product candidates, including: ivosidenib, enasidenib, vorasidenib, mitapivat, AG-270 and AG-636;
- continue our research and preclinical development of our product candidates;
- seek to identify additional product candidates;
- seek marketing approvals for our product candidates that successfully complete clinical trials;
- establish and maintain a sales, marketing and distribution infrastructure to commercialize any medicines for which we have or may obtain marketing approval;
- require the manufacture of larger quantities of product candidates for clinical development and, potentially, commercialization;
- maintain, expand and protect our intellectual property portfolio;
- hire additional clinical, quality control and scientific personnel;
- add additional personnel to support our product development and planned future commercialization efforts and our operations;
- add equipment and physical infrastructure to support our research and development; and
- acquire or in-license other medicines and technologies.

To become and remain profitable, we must develop and eventually commercialize one or more medicines with significant market potential. This will require us to be successful in a range of challenging activities, including completing preclinical testing and clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those medicines for which we may obtain marketing approval and satisfying any post-marketing requirements. Notwithstanding the extent to which we may succeed in these activities, we may never generate revenues that are significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our company could also cause our stockholders to lose all or part of their investment.

We will need substantial additional funding. If we are unable to raise capital when needed, we would be forced to delay, reduce or eliminate our product development programs or commercialization efforts.

We expect to incur significant expenses as we continue to advance our ongoing activities, particularly as we continue the research and development of, initiate and continue clinical trials of, seek marketing approvals for, and potentially

commercialize our product candidates, to the extent that such expenses are not the responsibility of Celgene or other collaborators. For example, we have incurred and expect to continue to incur expenses related to the commercialization of TIBSOVO®, and expect to incur expenses in connection with the buildout of a limited commercial infrastructure in the EU. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce or eliminate our research and development programs or future commercialization efforts.

We expect that our existing cash, cash equivalents and marketable securities as of December 31, 2019, together with anticipated product and royalty revenue, anticipated interest income and anticipated expense reimbursements under our collaboration agreements, but excluding any additional collaboration-related payments, will enable us to fund our operating expenses and capital expenditure requirements through at least the end of 2021. Our estimate as to how long we expect our existing cash, cash equivalents, and marketable securities to be available to fund our operations is based on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. Further, changing circumstances, some of which may be beyond our control, could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional funds sooner than planned. Our future capital requirements will depend on many factors, including:

- the scope, progress, results and costs of drug discovery, preclinical development, laboratory testing and clinical trials for our product candidates;
- the success of, and developments regarding, our collaborations;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- commercialization expenses relating to approved medicines such as TIBSOVO® and IDHIFA®;
- levels of product revenue from sales of TIBSOVO® and royalties on sales IDHIFA®;
- the cost associated with preparation for the potential commercial launch of one or more of our product candidates, including the build-out of a limited commercial infrastructure in the EU;
- our ability to establish and maintain additional collaborations on favorable terms, if at all; and
- the extent to which we acquire or in-license other medicines and technologies.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain additional marketing approvals and achieve product sales. In addition, TIBSOVO®, IDHIFA®, or other product candidates, if approved, may not achieve commercial success. Even if we succeed in developing and commercializing one or more of our product candidates, we may never achieve sufficient sales revenue to achieve or maintain profitability. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all.

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

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements. We do not have any committed external source of funds, other than our collaborations, which are limited in scope and duration. To the extent that we raise additional capital through the sale of equity or convertible debt securities, ownership interests will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, may require us to enter into agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. In addition, securing financing could require a substantial amount of time and attention from our management and may divert a disproportionate amount of their attention away from day-to-day activities, which may adversely affect our management's ability to oversee the development of our product candidates.

If we raise funds through additional collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable to us.

Our short operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

We were incorporated in the second half of 2007 and commenced operations in late 2008. Our operations to date have been primarily limited to organizing and staffing our company, business planning, raising capital, acquiring and developing our

technology, identifying potential product candidates, undertaking preclinical and clinical studies of our product candidates, and establishing a commercial infrastructure. All of our product candidates are still in preclinical and clinical development, with the exception of TIBSOVO® and IDHIFA®. Typically, it takes about 10 to 15 years to develop one new medicine from the time it is discovered to when it is available for treating patients, assuming that it successfully completes all stages of research and development and achieves marketing approval, all of which is highly uncertain. Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history.

We may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors that may adversely affect our ability to successfully commercialize our products and product candidates. We are in the early stages of transitioning from a company with solely a research focus to a company capable of supporting commercial activities and we have not yet demonstrated our ability to conduct large-scale sales and marketing activities necessary for successful commercialization. We may not be successful in such a transition.

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

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

We may not be successful in our commercialization of TIBSOVO®. If we do not successfully commercialize TIBSOVO® for the treatment of adult patients with R/R AML with a susceptible IDH1 mutation, our future prospects may be substantially harmed.

In July 2018, the FDA approved TIBSOVO® for the treatment of adult patients with R/R AML with a susceptible IDH1 mutation, and in May 2019, the FDA approved TIBSOVO® for the treatment of adult patients with newly diagnosed AML with a susceptible IDH1 mutation who are at least 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy. We are still evaluating ivosidenib in other clinical trials for the treatment of IDH1 mutant-positive cancers. Our ability to generate product revenue from TIBSOVO® will depend heavily on our successful development and commercialization of the product.

The development and commercialization of TIBSOVO® (ivosidenib) could be unsuccessful if:

- TIBSOVO® becomes no longer accepted as safe, efficacious, and cost-effective for the treatment of adult patients with R/R AML with a susceptible IDH1 mutation in the medical community and by third-party payors;
- we fail to maintain the necessary financial resources and expertise to manufacture, market and sell TIBSOVO®;
- we fail to continue to develop and implement effective marketing, sales and distribution strategies and operations for the development and commercialization of TIBSOVO®;
- we fail to continue to develop, validate and maintain a commercially viable manufacturing process for TIBSOVO® that is compliant with current good manufacturing practices;
- we fail to successfully obtain third party reimbursement and generate commercial demand that results in sales of TIBSOVO®;
- we encounter any third party patent interference, derivation, inter partes review, post-grant review, reexamination or patent infringement claims with respect to ivosidenib;
- we fail to comply with regulatory and legal requirements applicable to the sale of TIBSOVO®;
- competing drug products are approved for the same indications as TIBSOVO®;
- new significant safety risks are identified;
- ivosidenib does not demonstrate acceptable safety and efficacy in current or future clinical trials, or otherwise does not meet applicable regulatory standards for approval in indications other than for the treatment of adult patients with R/R AML with a susceptible IDH1 mutation and the treatment of adult patients with newly diagnosed AML with a susceptible IDH1 mutation who are at least 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.

If we experience significant delays or an inability to successfully develop and commercialize TIBSOVO® (ivosidenib), our business would be materially harmed.

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

A key element of our strategy is to identify and test compounds that target cellular metabolism and adjacent areas of biology in a variety of different types of hematologic malignancies, solid tumors and RGDs, as well as in immune cells for the treatment of cancer. A significant portion of the research that we are conducting involves new compounds and drug discovery methods, including our proprietary technology. The drug discovery that we are conducting using our proprietary technology may not be

successful in identifying compounds that are useful in treating cancer or RGDs. In addition, our efforts in the emerging field of metabolic immuno-oncology may not be as successful as our efforts to date in cancer metabolism and RGDs. Furthermore, our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for a number of reasons, including:

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

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

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

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

Our scientific approach focuses on using our proprietary technology to identify key metabolic enzymes in cancer, RGDs, or other diseased cells in the laboratory and then using these key enzymes to screen for and identify product candidates targeting cellular metabolism and adjacent areas of biology. We are also focused on metabolic immuno-oncology, an emerging field of cancer research focused on altering the metabolic state of immune cells to enhance the body's immune response to cancer.

Our focus on using our proprietary technology to screen for and identify product candidates targeting cellular metabolism and adjacent areas of biology may not result in the discovery and development of commercially viable medicines to treat cancer or RGDs. Any medicines that we develop may not effectively correct metabolic pathways or alter the metabolic state of immune cells. If we are able to develop a product candidate that targets cellular metabolism in preclinical studies, we may not succeed in demonstrating safety and efficacy of the product candidate in human clinical trials. In addition, even if we obtain marketing approval for one of our product candidates, we can provide no assurance that commercialization of such product candidate will be successful.

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

Other than TIBSOVO®, IDHIFA®, vorasidenib, mitapivat, AG-270 and AG-636, we have not commenced clinical trials for any of our other product candidates. Our ability to generate product revenue will depend heavily on the successful development and eventual commercialization of our product candidates.

The success of ivosidenib and our other product candidates will depend on many factors, including the following:

- successful enrollment in, and completion of, clinical trials;
- safety, tolerability and efficacy profiles that are satisfactory to the FDA, the EMA or any comparable foreign regulatory authority for marketing approval;
- timely receipt of marketing approvals from applicable regulatory authorities;
- establishing both clinical and commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- the performance of any collaborators;
- obtaining and maintaining patent and trade secret protection and non-patent exclusivity for our medicines;
- launching commercial sales of the medicines, if and when approved, whether alone or in collaboration with others;
- acceptance of the medicines, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies;
- continuing acceptable safety profile for the medicines following approval;
- enforcing and defending intellectual property rights and claims; and
- achieving desirable medicinal properties for the intended indications.

Many of these factors are beyond our control, including clinical development, the regulatory submission process, potential threats to our intellectual property rights and the manufacturing, marketing and sales efforts of any collaborator. If we or any collaborators do not achieve one or more of these factors in a timely manner or at all, we or such collaborators could experience

significant delays or an inability to successfully commercialize our most advanced product candidates, which would materially harm our business.

If clinical trials of products or product candidates fail to demonstrate safety and efficacy to the satisfaction of regulatory authorities or do not otherwise produce positive results, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of our product candidates.

We, and any collaborators, are not permitted to commercialize, market, promote or sell any product candidate in the United States without obtaining marketing approval from the FDA. Foreign regulatory authorities, such as the EMA, impose similar requirements. Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. In June 2018 Celgene submitted an MAA to the EMA for IDHIFA® for IDH2 mutant-positive AML, which it subsequently withdrew in December 2019. In December 2018, we submitted an MAA to the EMA for TIBSOVO® for the treatment of adult patients with IDH1 mutant-positive R/R AML and we plan to submit an sNDA for TIBSOVO® for previously treated IDH1 mutant-positive cholangiocarcinoma to the FDA by the end of 2020. However, we can provide no assurance that we will successfully submit such sNDA, or any NDA for any of our other product candidates, or that any MAA, NDA or sNDA submitted by us or Celgene will receive regulatory approval on the timeframe we expect, or at all.

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

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

Any inability to successfully complete preclinical and clinical development could result in additional costs to us, or any collaborators, and impair our ability to generate revenue from product sales, regulatory and commercialization milestones and royalties. Moreover, if we or our collaborators are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we or our collaborators are unable to successfully complete clinical trials of our product candidates or other testing, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we or our collaborators may:

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

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

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

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

- regulators or institutional review boards may not authorize us, our collaborators or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we or our collaborators may have delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- clinical trials of our product candidates may produce negative or inconclusive results, and we or our collaborators may decide, or regulators may require us, to conduct additional clinical trials, including testing in more subjects, or abandon product development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate; enrollment in these clinical trials, which may be particularly challenging for some of the orphan diseases we target in our RGD programs, may be slower than we anticipate; or participants may drop out of these clinical trials at a higher rate than we anticipate;
- third-party contractors used by us or our collaborators may fail to comply with regulatory requirements or meet their contractual obligations in a timely manner, or at all;
- we or our collaborators might have to suspend or terminate clinical trials of our product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks;
- regulators, institutional review boards, or the data safety monitoring board for such trials may require that we, our collaborators or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- the cost of clinical trials of our product candidates may be greater than anticipated;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate; and
- our product candidates may have undesirable side effects or other unexpected characteristics, causing us, our collaborators or our investigators, regulators or institutional review boards to suspend or terminate the trials.

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

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

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

Patient enrollment is also affected by other factors including:

- severity of the disease under investigation;
- availability and efficacy of approved medications for the disease under investigation;
- eligibility criteria for the study in question;
- perceived risks and benefits of the product candidate under study;
- efforts to facilitate timely enrollment in clinical trials;
- patient referral practices of physicians;

- the ability to monitor patients adequately during and after treatment; and
- proximity and availability of clinical trial sites for prospective patients.

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

In addition, other companies are conducting clinical trials, or may in the future conduct clinical trials, which may have similar eligibility criteria as our current or future clinical trials. For example, Daiichi Sankyo Company, Ltd., with DS-1001b, Bayer AG, or Bayer, with BAY1436032, and Forma Therapeutics Holdings, LLC, or Forma, with FT-2102, are conducting clinical trials that are targeted specifically towards patients with IDH1 mutant positive-cancers and/or include IDH mutant positive populations; companies such as ASLAN Pharmaceuticals Limited, or ASLAN, Bayer, Clear Creek Bio and PTC Therapeutics, Inc., or PTC, are clinically evaluating DHODH inhibitors for the treatment of hematologic malignancies; Rocket Pharma LTD is in the preclinical stages of development for a gene therapy targeting PK deficiency; Forma is developing a PKR activator for the treatment of hemolytic anemias; and IDEAYA Biosciences, Inc., or IDEAYA, is developing a MAT2A inhibitor for the treatment of MTAP-deleted cancers. As these companies and others initiate and conduct clinical trials, they may compete for eligible patients with our clinical trials of our product candidates. Competition for these patients may make it particularly difficult for us to enroll enough patients to complete our clinical trials for our product candidates in a timely and cost-effective manner.

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

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

With the exception of TIBSOVO® and IDHIFA®, all of our most advanced product candidates are still in clinical stage development and their risk of failure is high. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive marketing approval. Adverse events or undesirable side effects caused by, or other unexpected properties of, our product candidates could cause us or any collaborators, an institutional review board or regulatory authorities to interrupt, delay or halt clinical trials of one or more of our product candidates and could result in a more restrictive label, or the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities. If adverse effects were to arise in patients being treated with any of our product candidates, it could require us to halt, delay or interrupt clinical trials of such product candidate or adversely affect our ability to obtain requisite approvals to advance the development and commercialization of such product candidate. If any of our product candidates is associated with adverse events or undesirable side effects or has properties that are unexpected, we, or any collaborators, may need to abandon development or limit development of that product candidate to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Many compounds that initially showed promise in earlier stage testing for treating cancer, RGDs or other diseases have later been found to cause side effects that prevented further development of the compound. For instance, in December 2016, we withdrew our IND for AG-519, our second PKR activator, following verbal notification of a clinical hold from the FDA relating to a previously disclosed case of drug-induced cholestatic hepatitis which occurred in our phase 1 clinical trial of AG-519 in healthy volunteers. Although these decisions and this hepatic adverse event finding do not affect our ongoing clinical trials for mitapivat, we cannot provide any assurances that there will not be similar or other treatment-related severe adverse events in our other clinical trials for mitapivat, that our other trials will not be placed on clinical hold in the future, or that patient recruitment for our other trials will not be adversely impacted.

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

The outcome of preclinical studies and early clinical trials may not be predictive of the success of later clinical trials, and interim results of clinical trials do not necessarily predict success in future clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in

earlier development, and we could face similar setbacks. The design of a clinical trial can determine whether its results will support approval of a product and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. We have limited experience in designing clinical trials and may be unable to design and execute a clinical trial to support marketing approval. In addition, preclinical and clinical data are often susceptible to varying interpretations and analyses. Many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval for the product candidates. Even if we, or any collaborators, believe that the results of clinical trials for our product candidates warrant marketing approval, the FDA or comparable foreign regulatory authorities may disagree and may not grant marketing approval of our product candidates.

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

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

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

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

Because we are focused on precision medicine, in which predictive biomarkers will be used to identify the right patients for our drug candidates, we believe that our success will depend, in part, on our ability to develop companion diagnostics, which are assays or tests to identify an appropriate patient population for these drug candidates. There has been limited success to date industry-wide in developing these types of companion diagnostics. To be successful, we need to address a number of scientific, technical and logistical challenges. We have little experience in the development of diagnostics and may not be successful in developing appropriate diagnostics to pair with any of our therapeutic product candidates that receive marketing approval. Companion diagnostics are subject to regulation by the FDA and similar regulatory authorities outside the United States as medical devices and require separate regulatory approval prior to commercialization. Given our limited experience in developing diagnostics, we rely and expect to continue to rely in part or in whole on third parties for their design and manufacture. We also depend on Celgene and Abbott Laboratories for the development of the FDA approved companion diagnostics for IDHIFA® and TIBSOVO®, respectively, and may in the future depend on Celgene or other third parties for the development of other companion diagnostics for our cancer therapeutic product candidates. If any parties, including without limitation Celgene or us, or any third parties engaged by Celgene or us are unable to successfully develop companion diagnostics for our therapeutic product candidates, or experience delays in doing so:

- the development of our therapeutic product candidates may be adversely affected if we are unable to appropriately select patients for enrollment in our clinical trials;
- our therapeutic product candidates may not receive marketing approval if safe and effective use of a therapeutic product candidate depends on an in vitro diagnostic; and
- we may not realize the full commercial potential of any therapeutics that receive marketing approval if, among other reasons, we are unable to appropriately select patients who are likely to benefit from therapy with our medicines.

As a result of any of these events, our business would be harmed, possibly materially.

We may be unable to obtain, or may be delayed in obtaining, marketing approval for our product candidates.

It is possible that the FDA or EMA may refuse to accept for substantive review any NDA, sNDA or MAA that we and/or Celgene submit for our product candidates, or may conclude after review of our data that our application is insufficient to obtain marketing approval of our product candidates. If the FDA or EMA does not accept or approve our applications for any of our product candidates, it may require that we conduct additional clinical trials, preclinical studies or manufacturing validation studies and submit that data before it will reconsider our applications. Depending on the extent of these or any other FDA- or

EMA-required trials or studies, approval of any applications that we submit may be delayed by several years, or may require us to expend more resources than we have available. It is also possible that additional trials or studies, if performed and completed, may not be considered sufficient by the FDA or EMA to approve our applications. For example, Celgene withdrew its MAA with the EMA for IDHIFA® for IDH2 mutant-positive AML in December 2019. Any delay in obtaining, or an inability to obtain, marketing approvals would prevent us or Celgene from commercializing our product candidates, generating revenue and achieving and sustaining profitability. If any of these outcomes occur, we may be forced to abandon our development efforts for our product candidates, which could significantly harm our business.

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

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

- regulatory authorities may withdraw their approval of the product or seize the product;
- we, or any collaborators, may be required to recall the product, change the way the product is administered or conduct additional clinical trials;
- additional restrictions may be imposed on the marketing of, or the manufacturing processes for, the particular product;
- we may be subject to fines, injunctions or the imposition of civil or criminal penalties;
- regulatory authorities may require the addition of labeling statements, such as a "black box" warning or a contraindication, including, for example, the black box warning for differentiation syndrome on the labels for IDHIFA® and TIBSOVO®;
- we, or any collaborators, may be required to create a Medication Guide outlining the risks of the previously unidentified side effects for distribution to patients;
- we, or any collaborators, could be sued and held liable for harm caused to patients;
- the product may become less competitive; and
- our reputation may suffer.

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

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

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

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

We have limited experience in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for any approved medicine for which we retain sales and marketing responsibilities, we must either develop a sales and marketing organization or outsource these functions to other third parties. Although we have established sales and marketing

capabilities to support our co-promotion efforts for IDHIFA® and our sales of TIBSOVO®, we will need to further build our sales and marketing infrastructure to sell, or participate in sales activities with our collaborators for, our other product candidates if and when they are approved, including, for example, to support the potential approval of one or more product candidates in the EU.

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

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

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future medicines;
- the lack of complementary medicines to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

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

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

The development and commercialization of new drug products is highly competitive. We face competition with respect to our current products and product candidates, and we and our collaborators will face competition with respect to any product candidates that we or they may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of the disease indications for which we are developing our product candidates, such as AML and high risk myelodysplasia. For example, Jazz Pharmaceuticals plc, Abbvie Inc. (in collaboration with Roche Holdings Inc.), Novartis International AG, Pfizer, Inc. and Astellas Pharma Inc. are each marketing therapies to treat AML, Acceleron Pharma Inc. and bluebird bio, Inc. are each marketing therapies to treat beta thalassemia, and a number of other biotechnology companies have product candidates in clinical development in similar indications as ours. Some competitive products and therapies are based on scientific approaches that are the same as or similar to our approach, and others are based on entirely different approaches, for example, in the area of RGDs. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

We are developing most of our initial product candidates for the treatment of cancer. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy, and cancer drugs are frequently prescribed off-label by healthcare professionals. Some of the currently approved drug therapies are branded and subject to patent protection, and others are available on a generic basis. Many of these approved drugs are well established therapies and are widely accepted by physicians, patients and third-party payors. Insurers and other third-party payors may also encourage the use of generic products. We expect that our product candidates, if approved, will be priced at a significant premium over competitive generic products, as is the case with TIBSOVO® and IDHIFA®. This may make it difficult for us to achieve our business strategy of using our product candidates in combination with existing therapies or replacing existing therapies with our product candidates.

We are also pursuing product candidates to treat patients with RGDs. There are a variety of treatment options available, including a number of marketed enzyme replacement therapies, for treating patients with RGDs. In addition to currently marketed therapies, there are also a number of products that are either enzyme replacement therapies or gene therapies in various stages of clinical development to treat RGDs. These products in development may provide efficacy, safety, convenience

and other benefits that are not provided by currently marketed therapies. As a result, they may provide significant competition for any of our product candidates for which we obtain marketing approval.

There are also a number of product candidates in preclinical or clinical development by third parties to treat hematologic malignancies, solid tumors and RGDs by targeting similar mechanisms of action as our product candidates. These companies include large pharmaceutical companies, such as AstraZeneca plc, Bayer, Daiichi Sankyo, Eli Lilly and Company, Roche and its subsidiary Genentech, Inc., GlaxoSmithKline plc, Merck, and Pfizer, as well as biotechnology companies of various sizes, such as Forma, ASLAN, Clear Creek Bio, IDEAYA, PTC and Rocket Pharma. In addition, there are several companies developing immunotherapies, including metabolic immunotherapies, targeting cancer, including AstraZeneca; BeiGene, Ltd.; Bristol-Myers Squibb Company; GlaxoSmithKline; Genentech; and Merck. Our competitors may develop products that are more effective, safer, more convenient or less costly than any that we are developing or that would render our product candidates obsolete or non-competitive. In addition, our competitors may discover biomarkers that more efficiently measure metabolic pathways than our methods, which may give them a competitive advantage in developing potential products. Our competitors may also obtain marketing approval from the FDA or other regulatory authorities for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market.

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

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

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

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

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

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

The commercial success of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by third-party payors, including government health administration authorities and private health coverage insurers. If coverage and reimbursement is not available, or reimbursement is available only to limited levels, we, or any collaborators, may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us, or any future collaborators, to

establish or maintain pricing sufficient to realize a sufficient return on our or their investments. In the United States, no uniform policy of coverage and reimbursement for products exists among third-party payors and coverage and reimbursement for products can differ significantly from payor to payor. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

There is significant uncertainty related to third-party payor coverage and reimbursement of newly approved drugs. Marketing approvals, pricing and reimbursement for new drug products vary widely from country to country. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we, or any collaborators, might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay commercial launch of the product, possibly for lengthy time periods, which may negatively impact the revenue we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability or the ability of any collaborators to recoup our or their investment in one or more product candidates, even if our product candidates obtain marketing approval.

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

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

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

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

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

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

- loss of revenue;
- reduced resources of our management to pursue our business strategy; and
- the inability to commercialize any medicines that we may develop.

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

Our internal computer systems, or those of any third parties with which we contract, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

Despite the implementation of security measures, our internal computer systems and those of third parties with which we contract are vulnerable to damage from computer viruses, worms and other destructive or disruptive software, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. Such systems are also vulnerable to service interruptions or to security breaches from inadvertent or intentional actions by our employees, third-party vendors and/or business partners, or from cyber attacks by malicious third parties. Cyber incidents are increasing in their frequency, sophistication and intensity, and have become increasingly difficult to detect. Cyber incidents could include the deployment of harmful malware, ransomware, denial-of-service attacks, unauthorized access to or deletion of files, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information. Cyber incidents also could include phishing attempts or e-mail fraud to cause payments or information to be transmitted to an unintended recipient. We could be subject to risks caused by misappropriation, misuse, leakage, falsification or intentional or accidental release or loss of information maintained in the information systems and networks of our company, including personal information of our employees.

System failures, accidents, cyber attacks or security breaches could cause interruptions in our operations, and could result in a material disruption of our clinical and commercialization activities and business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions, in addition to possibly requiring substantial expenditures of resources to remedy. For example, the loss of clinical trial data from completed or future trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our competitive position could be harmed and our product research, development and commercialization efforts could be delayed. In addition, we may not have adequate insurance coverage to provide compensation for any losses associated with such events.

If a material breach of our security or that of our vendors occurs, the market perception of the effectiveness of our security measures could be harmed, we could lose business and our reputation and credibility could be damaged. We could be required to expend significant amounts of money and other resources to repair or replace information systems or networks. Although we develop and maintain systems and controls designed to prevent these events from occurring, and we have a process to identify and mitigate threats, the development and maintenance of these systems, controls and processes is costly and requires ongoing monitoring and updating as technologies change and efforts to overcome security measures become more sophisticated. Moreover, despite our efforts, the possibility of these events occurring cannot be eliminated entirely

Compliance with global privacy and data security requirements could result in additional costs and liabilities to us or inhibit our ability to collect and process data globally, and the failure to comply with such requirements could subject us to significant fines and penalties, which may have a material adverse effect on our business, financial condition or results of operations.

The regulatory framework for the collection, use, safeguarding, sharing, transfer and other processing of information worldwide is rapidly evolving and is likely to remain uncertain for the foreseeable future. Globally, virtually every jurisdiction in which we operate has established its own data security and privacy frameworks with which we must comply. For example, the collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the EU, including personal health data, is subject to EU General Data Protection Regulation, or the GDPR, which took effect across all member states of the European Economic Area, or EEA, in May 2018. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to: processing health and other sensitive data; obtaining consent of individuals to whom the personal health data relates; providing information to individuals regarding data processing activities; implementing safeguards to protect the security and confidentiality of personal data; providing notification of data breaches; and taking certain measures when engaging third-party processors. The GDPR increases our obligations with respect to clinical trials conducted in the EEA by expanding the definition of personal data to include coded data and requiring changes to

informed consent practices and more detailed notices for clinical trial subjects and investigators. In addition, the GDPR also imposes strict rules on the transfer of personal data to countries outside the EU, including the United States and, as a result, increases the scrutiny that clinical trial sites located in the EEA should apply to transfers of personal data from such sites to countries that are considered to lack an adequate level of data protection, such as the United States. The GDPR also permits data protection authorities to require destruction of improperly gathered or used personal information and/or impose substantial fines for violations of GDPR, which can be up to four percent of global revenues or 20 million Euros, whichever is greater, and it also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies and obtain compensation for damages resulting from violations of GDPR. In addition, the GDPR provides that EU member states may make their own further laws and regulations limiting the processing of personal data, including genetic, biometric or health data.

Given the breadth and depth of changes in data protection obligations, preparing for and complying with the GDPR's requirements is rigorous and time intensive and requires significant resources and a review of our technologies, systems and practices, as well as those of any third-party collaborators, service providers, contractors or consultants that process or transfer personal data collected in the EU. The GDPR and other changes in laws or regulations associated with the enhanced protection of certain types of sensitive data, such as healthcare data or other personal information from our clinical trials, could require us to change our business practices and put in place additional compliance mechanisms, may interrupt or delay our development, regulatory and commercialization activities and increase our cost of doing business, and could lead to government enforcement actions, private litigation and significant fines and penalties against us and could have a material adverse effect on our business, financial condition or results of operations. Similarly, failure to comply with federal and state laws regarding privacy and security of personal information could expose us to fines and penalties under such laws. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our reputation and our business.

Similar privacy and data security requirements are either in place or underway in the United States. There are a broad variety of data protection laws that may be applicable to our activities, and a range of enforcement agencies at both the state and federal levels that can review companies for privacy and data security concerns based on general consumer protection laws. The Federal Trade Commission and state Attorneys General all are aggressive in reviewing privacy and data security protections for consumers. New laws also are being considered at both the state and federal levels. For example, the California Consumer Privacy Act, which goes into effect in 2020, is creating similar risks and obligations as those created by GDPR. Many other states are considering similar legislation. A broad range of legislative measures also have been introduced at the federal level. Accordingly, failure to comply with current and any future federal and state laws regarding privacy and security of personal information could expose us to fines and penalties. We also face a threat of consumer class actions related to these laws and the overall protection of personal data. Even if we are not determined to have violated these laws, investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our reputation and our business.

Risks Related to Our Dependence on Third Parties

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

In August 2017, the FDA approved IDHIFA® for the treatment of adult patients with R/R AML and an IDH2 mutation, on the basis of an NDA submitted by Celgene. Although IDHIFA® has received FDA approval in R/R AML with an IDH2 mutation, we and Celgene are still evaluating enasidenib in other clinical trials. Celgene maintains worldwide development and commercial rights to IDHIFA® and will fund the development and commercialization costs related to this program, although we have certain co-commercialization and co-promotion rights to IDHIFA®. Under the 2010 Agreement, Celgene is responsible for all development costs for enasidenib, and we are eligible to receive up to $80.0 million in milestone payments and a tiered royalty on any net sales of products containing IDHIFA®. Thus, our ability to generate revenue from IDHIFA® will depend heavily on Celgene's successful development and eventual commercialization of the product.

The development and continued commercialization of IDHIFA® (enasidenib) could be unsuccessful if:

- IDHIFA® becomes no longer accepted as safe, efficacious, and cost-effective for the treatment of adult patients with R/R AML and an IDH2 mutation in the medical community and by third-party payors;
- Celgene fails to continue to apply the necessary financial resources and expertise to manufacturing, marketing and selling IDHIFA®;
- Celgene does not continue to develop and implement effective marketing, sales and distribution strategies and operations for development and commercialization of IDHIFA®;

- Celgene does not continue to develop, validate and maintain a commercially viable manufacturing process for IDHIFA® that is compliant with current good manufacturing practices;
- Celgene does not successfully obtain third party reimbursement and generate commercial demand that results in sales of IDHIFA®;
- Celgene fails to provide us with timely and accurate information regarding development, sales and marketing activities;
- we or Celgene encounter any third party patent interference, derivation, inter partes review, post-grant review, reexamination or patent infringement claims with respect to enasidenib;
- Celgene does not comply with regulatory and legal requirements applicable to the sale of IDHIFA®;
- competing drug products are approved for the same indications as IDHIFA®;
- new safety risks are identified;
- enasidenib does not demonstrate acceptable safety and efficacy in current or future clinical trials, or otherwise does not meet applicable regulatory standards for approval in indications other than for the treatment of adult patients with R/R AML and an IDH2 mutation; or
- Celgene does not maintain or defend intellectual property rights associated with enasidenib.

We also face the risk that Celgene could determine to reprioritize its commercial or development programs and reduce or terminate its efforts on the development or commercialization of IDHIFA®. For example, Bristol-Myers Squibb, or BMS, acquired Celgene in November 2019. BMS may not retain and motivate key personnel who are important to the continued development of the programs under our agreements with Celgene. In addition, BMS could determine to reprioritize Celgene's development programs such that it ceases to diligently pursue the development of our programs, and/or cause the agreements between Celgene and us to terminate.

If we or Celgene experience significant delays or an inability to successfully develop and continue to commercialize IDHIFA® (enasidenib), our business would be materially harmed.

The failure to maintain the CStone Agreement or the failure of CStone to perform its obligations under the CStone Agreement, could negatively impact our business prospects in the CStone Territory.

In June 2018, we entered into the CStone Agreement, for the development and commercialization of ivosidenib, either as monotherapy or in combination with other therapies, in the CStone Territory. Pursuant to the CStone Agreement, CStone will be responsible for the development and commercialization of ivosidenib in the CStone Territory. Our ability to generate royalty and milestone revenue under the CStone Agreement is dependent on CStone's performance of its obligations under the agreement. We cannot control the amount and timing of resources that CStone will dedicate to these efforts.

We are subject to a number of other risks associated with our dependence on the CStone Agreement with respect to ivosidenib in the CStone Territory, including:

- CStone may fail to comply with applicable regulatory guidelines with respect to developing, manufacturing or commercializing ivosidenib, which could adversely impact future development or potential sales of ivosidenib in the CStone Territory or elsewhere;
- We and CStone could disagree as to future development plans and CStone may delay, fail to commence or stop future clinical trials or other development;
- There may be disputes between CStone and us, including disagreements regarding the CStone Agreement, that may result in the delay of or failure to achieve developmental, regulatory and sales objectives that would result in milestone or royalty payments, the delay or termination of any future development or commercialization of ivosidenib in the CStone Territory, and/or costly litigation or arbitration that diverts our management's attention and resources;
- CStone may fail to provide us with timely and accurate information regarding development, sales and marketing activities or supply forecasts, which could adversely impact our ability to comply with our obligations to CStone, as well as our ability to generate accurate financial forecasts; and
- Business combinations, significant changes in CStone's business strategy, or the impact of public health epidemics, such as the coronavirus currently impacting China and elsewhere, may adversely affect CStone's ability or resources available to perform its obligations under the CStone Agreement.

The CStone Agreement is also subject to early termination, including through CStone's right under certain circumstances to terminate upon advance notice to us. If the CStone Agreement is terminated early, we may not be able to find another collaborator for the further development and commercialization of ivosidenib in the CStone Territory on acceptable terms, or at all, and we may be unable to pursue continued development and commercialization of ivosidenib in the CStone Territory on our own.

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

We are party to several collaboration agreements, including the 2010 Agreement and the 2016 Agreement with Celgene, and the CStone Agreement. These collaborations involve complex allocations of rights, provide for milestone payments to us based on the achievement of specified clinical development, regulatory and commercial milestones, provide us with royalty-based revenue if certain product candidates are successfully commercialized and provide for cost reimbursements of certain development activities. We cannot predict the success of these collaborations.

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

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

- Collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations. Under the 2010 Agreement, programs under a co-development and co-commercialization agreement pursuant to the 2016 Agreement and the CStone Agreement, development and commercialization plans and strategies for licensed programs, such as enasidenib, or in the CStone Territory, ivosidenib, will be conducted in accordance with a plan and budget approved by a joint committee comprised of equal numbers of representatives from each of us and Celgene or CStone, as to which Celgene or CStone, as applicable, may have final decision-making authority.
- Collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborator's strategic focus or available funding or external factors such as an acquisition that diverts resources or creates competing priorities. For example, under the 2016 Agreement, it is possible for Celgene to elect not to progress into preclinical development a product candidate that we have nominated and the joint research committee confirmed, without triggering a termination of the collaboration arrangement.
- Collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing, which may result in a need for additional capital to pursue further development or commercialization of the applicable product candidate. For example, under the 2010 Agreement and the 2016 Agreement, it is possible for Celgene to terminate the agreement, upon 90 days prior written notice, with respect to any product candidate at any point in the research, development and clinical trial process, without triggering a termination of the remainder of the collaboration arrangement.
- Collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our medicines or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours.
- Collaborators with marketing and distribution rights to one or more medicines may not commit sufficient resources to the marketing and distribution of such medicine or medicines.
- Collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our proprietary information or expose us to potential litigation. For example, under specified circumstances Celgene has the first right to maintain or defend our intellectual property rights with respect to enasidenib under the 2010 Agreement and, although we may have the right to assume the maintenance and defense of our intellectual property rights if Celgene does not, our ability to do so may be compromised by Celgene's actions.
- Disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of our medicines or product candidates or that result in costly litigation or arbitration that diverts management attention and resources.
- We may lose certain valuable rights under circumstances identified in our collaborations, including, in the case of our agreements with Celgene, if we undergo a change of control.
- Collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates. For example, in September 2018, we and Celgene agreed to terminate the AG-881 Agreements effective as of September 4, 2018, as a result of which we will be responsible for future development costs of vorasidenib, other than certain agreed-up costs which we and Celgene had

split until December 31, 2018. Celgene can terminate its remaining agreements with us, in their entirety or with respect to enasidenib under the 2010 Agreement or any program under the 2016 Agreement, upon 90 days' notice and can terminate each entire agreement with us in connection with a material breach of the agreement by us that remains uncured for a period ranging from 60 to 90 days. CStone has the right, under certain circumstances, to terminate the CStone Agreement upon advance notice to us, and may, subject to specified cure periods, terminate the CStone Agreement in the event of our uncured material breach or under specified circumstances relating to our insolvency.

- Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all.
- If present or future collaborators of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program under such collaboration could be delayed, diminished or terminated. For example, BMS may not retain and motivate key personnel who are important to the continued development of the programs under our agreements with Celgene. In addition, BMS could determine to reprioritize Celgene's development programs such that it ceases to diligently pursue the development of our programs, and/or cause the agreements between Celgene and us to terminate.

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

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

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

We may also be restricted under existing collaboration agreements from entering into future agreements on certain terms with potential collaborators. For example, during the discovery phase of the 2016 Agreement, we may not directly or indirectly develop, manufacture or commercialize, except pursuant to the agreement, any medicine or product candidate with specified activity against certain metabolic targets except in connection with certain third-party collaborations or with respect to certain targets the rights to which have reverted back to us pursuant to the terms of the 2016 Agreement. Following the discovery phase until termination or expiration of the 2010 Agreement, either in its entirety or with respect to the relevant program, we may not directly or indirectly develop, manufacture or commercialize, outside of the collaboration, any medicine or product candidate with specified activity against any collaboration target that is within a licensed program or against any former collaboration target against which Celgene is conducting an independent program under the agreement. Following the discovery phase of the 2016 Agreement until termination or expiration of the applicable co-development and co-commercialization agreement or license agreement under the 2016 Agreement, we may not directly or indirectly develop, manufacture or commercialize, outside of the collaboration, any medicine or product candidate with specified activity against the collaboration target that is the subject of such co-development and co-commercialization agreement or license agreement, except in connection with certain third-party collaborations or with respect to certain targets the rights to which have reverted back to us pursuant to the terms of the 2016 Agreement. During the term of the CStone Agreement, we are prohibited from developing or commercializing, in the CStone Territory and in specified indications, other compounds or products that inhibit IDH1 mutations at specified levels of binding.

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

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

have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

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

We do not independently conduct clinical trials of any of our product candidates. We rely and expect to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials. In addition, we currently rely and expect to continue to rely on third parties to conduct some aspects of our research and preclinical testing. Any of these third parties may terminate their engagements with us, some in the event of an uncured material breach and some at any time. If any of our relationships with these third parties terminate, we may not be able to enter into arrangements with alternative third-parties or to do so on commercially reasonable terms. Switching or adding additional third parties involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new third party commences work. As a result, delays may occur in our product development activities. Although we seek to carefully manage our relationships with our CROs, we could encounter similar challenges or delays in the future and these challenges or delays could have a material adverse impact on our business, financial condition and prospects.

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

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

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

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

We do not have any manufacturing facilities. We currently rely, and expect to continue to rely, on third-party manufacturers for the manufacture of our product candidates for preclinical and clinical testing and for commercial supply of any of these product candidates for which we or our collaborators obtain marketing approval. To date, we have obtained materials for our product candidates for our ongoing preclinical and clinical testing from third-party manufacturers.

Although we have long-term supply agreements in place for commercial supply of TIBSOVO® with third-party manufacturers, we may be unable to establish any further long-term supply agreements with third-party manufacturers or to do so on

acceptable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

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

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

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

Public health epidemics, such as the coronavirus currently impacting China and elsewhere, may impact the ability of our existing or future manufacturers to perform their obligations to us.

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

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

Risks Related to Our Intellectual Property

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

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our proprietary medicines and technology. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our novel technologies and medicines that are important to our business. We do not yet have issued patents for all our most advanced product candidates in all markets we intend to commercialize.

The patent prosecution process is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. Although we enter into non-disclosure and confidentiality agreements with parties who have access to patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, contract research organizations, contract manufacturers, consultants, advisors and other third parties, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection.

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

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued that protect our technology or medicines or that effectively prevent others from commercializing competitive technologies and medicines. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value of our patents or narrow the scope of our patent protection. The laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore we cannot be certain that we were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions.

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

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

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

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

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

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

Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights and intellectual property of third parties. The biotechnology and pharmaceutical industries are characterized by extensive litigation regarding patents and other intellectual property rights. We have in the past and may in the future become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our medicines and technology, including interference proceedings before the USPTO. For example, in 2011, The Leonard and Madlyn Abramson Family Cancer Research Institute at the Abramson Cancer Center of the University of Pennsylvania initiated a lawsuit against us, one of our founders, Craig B. Thompson, M.D., and Celgene, alleging misappropriation of intellectual property and, in 2012, the Trustees of the University of Pennsylvania initiated a similar lawsuit against us and Dr. Thompson. Each of these lawsuits was settled in 2012. We are not aware of any other legal proceedings having been filed against us to date. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. If we or one of our

collaborators are found to infringe a third party's intellectual property rights, we or they could be required to obtain a license from such third party to continue developing and marketing our medicines and technology. However, we or our collaborators may not be able to obtain any required license on commercially reasonable terms or at all. Even if we or our collaborators were able to obtain a license, it could be non-exclusive, thereby giving our competitors and other third parties access to the same technologies licensed to us. We or our collaborators could be forced, including by court order, to cease developing and commercializing the infringing technology or medicine. In addition, we or our collaborators could be found liable for monetary damages. A finding of infringement could prevent us or our collaborators from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we or our collaborators have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

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

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

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

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

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

In addition to seeking patents for some of our technology and medicines, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. With respect to our proprietary cellular metabolism technology platform, we consider trade secrets and know-how to be our primary intellectual property. Trade secrets and know-how can be difficult to protect. In particular, we anticipate that with respect to this technology platform, these trade secrets and know-how will over time be disseminated within the industry through independent development, the publication of journal articles describing the methodology, and the movement of personnel skilled in the art from academic to industry scientific positions.

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

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

Even if we complete necessary preclinical studies and clinical trials, the marketing approval process is expensive, time-consuming and uncertain and may prevent us from obtaining approvals for the commercialization of some or all of our

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

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, record keeping, labeling, storage, approval, advertising, promotion, sale and distribution, export and import, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the EMA and comparable regulatory authorities in other countries. With the exception of IDHIFA® and TIBSOVO®, we and our collaborators have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction. Celgene submitted an MAA to the EMA for IDHIFA® for IDH2 mutant-positive AML which it subsequently withdrew in December 2019. We submitted an MAA to the EMA for TIBSOVO® for the treatment of adult patients with IDH1 mutant-positive R/R AML. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third-party contract research organizations to assist us in this process.

Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing regulatory approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use.

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

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

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

In order to market and sell our medicines in the EU and many other jurisdictions, we or our collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, a product must be approved for reimbursement before the product can be approved for sale in that country. We or our collaborators may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. For example, Celgene submitted an MAA to the EMA for IDHIFA® for IDH2 mutant-positive AML, which it subsequently withdrew in December 2019. We submitted an MAA to the EMA for TIBSOVO® for the treatment of adult patients with IDH1 mutant-positive R/R AML, Celgene or we may not be successful in obtaining EMA approval of IDHIFA® or TIBSOVO®, respectively, on a timely basis, or ever. Moreover, approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our medicines in any market.

Additionally, on June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the EU, commonly referred to as Brexit. Following protracted negotiations, the United Kingdom left the EU on January 31, 2020. Under the withdrawal agreement, there is a transitional period until December 31, 2020 (extendable up to two years). Discussions between the United Kingdom and the EU have so far mainly focused on finalizing withdrawal issues and transition agreements but have been extremely difficult to date. To date, only an outline of a trade agreement has been reached. Much remains open but the Prime Minister has indicated that the United Kingdom will not seek to extend the transitional period beyond the end of 2020. If no trade agreement has been reached before the end of the transitional period, there may be significant market and economic

disruption. The Prime Minister has also indicated that the United Kingdom will not accept high regulatory alignment with the EU.

Since the regulatory framework for pharmaceutical products in the United Kingdom covering quality, safety, and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales, and distribution of pharmaceutical products is derived from EU directives and regulations, Brexit could materially impact the future regulatory regime that applies to products and the approval of our product candidates in the United Kingdom. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom and/or the EU and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or EU for our product candidates, which could significantly and materially harm our business.

Furthermore, other European countries may seek to conduct referenda with respect to continuing membership with the EU. We do not know to what extent Brexit or other comparable initiatives, or any resulting changes, would affect our ability to conduct clinical trials or obtain marketing approval in these jurisdictions, and each could materially impact our ability to conduct clinical trials or obtain marketing approval on a timely basis, or at all.

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

In the United States, enasidenib and ivosidenib received fast track designation for treatment of patients with AML that harbor an IDH2 and IDH1 mutation, respectively. If a drug is intended for the treatment of a serious or life-threatening disease or condition and the drug demonstrates the potential to address unmet medical needs for this disease or condition, the drug sponsor may apply for FDA fast track designation. The FDA has broad discretion whether or not to grant fast track designation, so even if we believe a particular product candidate is eligible for such designation, the FDA may decide not to grant it. Even if our product candidates receive fast track designation, we may not experience a faster development process, review or approval, if at all, compared to conventional FDA procedures. The FDA may withdraw fast track designation if it believes that the designation is no longer supported by data from our clinical development program.

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

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

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

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

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

Any product candidate for which we or our collaborators obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such medicine, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and

other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to quality control and manufacturing, quality assurance and corresponding maintenance of records and documents, and requirements regarding the distribution of samples to physicians and record keeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the medicine may be marketed or to the conditions of approval, or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the medicine, including the requirement to implement a risk evaluation and mitigation strategy.

The FDA and other agencies, including the Department of Justice, or the DOJ, closely regulate and monitor the post-approval marketing and promotion of products to ensure that they are marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA and DOJ impose stringent restrictions on manufacturers' communications regarding off-label use and if we do not market our medicines for their approved indications, we may be subject to enforcement action for off-label marketing. Violations of the FDCA and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription drugs may lead to investigations and enforcement actions alleging violations of federal and state health care fraud and abuse laws, as well as state consumer protection laws, which violations may result in the imposition of significant administrative, civil and criminal penalties.

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

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

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

Our relationships with healthcare providers, physicians and third-party payors will be subject to applicable anti-kickback, fraud and abuse and other healthcare laws and regulations, which, in the event of a violation, could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

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

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation or arranging of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;
- the federal False Claims Act imposes criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, false or

fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per-claim penalties, currently set at $10,781.40 to $21,562.80 per false claim;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal Physician Payments Sunshine Act requires applicable manufacturers of covered drugs to report payments and other transfers of value to physicians and teaching hospitals; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws and transparency statutes, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and may require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

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

The provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is also prohibited in the EU. The provision of benefits or advantages to physicians is governed by the national anti-bribery laws of EU Member States, such as the U.K. Bribery Act 2010. Infringement of these laws could result in substantial fines and imprisonment.

Payments made to physicians in certain EU Member States must be publicly disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician's employer, his or her competent professional organization and/or the regulatory authorities of the individual EU Member States. These requirements are provided in the national laws, industry codes or professional codes of conduct, applicable in the EU Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

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

We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. For example, certain policies of the Trump Administration may impact our business and industry. Namely, the Trump Administration has taken several executive actions, including the issuance of a number of Executive Orders, that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. An under-staffed FDA could result in delays in the FDA's responsiveness or in its ability to review submissions or applications, issue regulations or guidance, or implement or enforce regulatory requirements in a timely fashion or at all.

For example, on January 30, 2017, President Trump issued an Executive Order, applicable to all executive agencies, including the FDA, which required that for each notice of proposed rulemaking or final regulation to be issued in fiscal year 2017, the agency shall identify at least two existing regulations to be repealed, unless prohibited by law. These requirements are referred to as the "two-for-one" provisions. This Executive Order includes a budget neutrality provision that required the total incremental cost of all new regulations in the 2017 fiscal year, including repealed regulations, to be no greater than zero, except

in limited circumstances. For fiscal years 2018 and beyond, the Executive Order requires agencies to identify regulations to offset any incremental cost of a new regulation and approximate the total costs or savings associated with each new regulation or repealed regulation. In interim guidance issued by the Office of Information and Regulatory Affairs within OMB on February 2, 2017, the administration indicates that the "two-for-one" provisions may apply not only to agency regulations, but also to significant agency guidance documents. In addition, on February 24, 2017, President Trump issued an executive order directing each affected agency to designate an agency official as a "Regulatory Reform Officer" and establish a "Regulatory Reform Task Force" to implement the two-for-one provisions and other previously issued executive orders relating to the review of federal regulations, however it is difficult to predict how these requirements will be implemented, and the extent to which they will impact the FDA's ability to exercise its regulatory authority. If these executive actions impose constraints on the FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted.

Current and future legislation may increase the difficulty and cost for us and any collaborators to obtain marketing approval and commercialize our drug candidates and affect the prices we, or they, may obtain.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could, among other things, prevent or delay marketing approval of our drug candidates, restrict or regulate post-approval activities and affect our ability, or the ability of any collaborators, to profitably sell any drugs for which we, or they, obtain marketing approval. We expect that current laws, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we, or any collaborators, may receive for any approved drugs.

Among the provisions of the Patient Protection and Affordable Care Act, or ACA, of potential importance to our business and our drug candidates are the following:

- an annual, non-deductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program;
- expansion of healthcare fraud and abuse laws, including the civil False Claims Act and the federal Anti-Kickback Statute, new government investigative powers and enhanced penalties for noncompliance;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts off negotiated prices to eligible beneficiaries during their coverage gap period, as a condition for a manufacturer's outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- new requirements to report certain financial arrangements with physicians and teaching hospitals;
- a new requirement to annually report drug samples that manufacturers and distributors provide to physicians; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

Other legislative changes have been proposed and adopted since the ACA was enacted. These changes include the Budget Control Act of 2011, which, among other things, led to aggregate reductions to Medicare payments to providers of up to 2% per fiscal year that started in 2013 and will stay in effect through 2024 unless additional Congressional action is taken, and the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Further, there have been several recent U.S. congressional inquiries and proposed state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products.

Since January 2017, President Trump has signed two Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. The second Executive Order terminates the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General

filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. The loss of the cost share reduction payments is expected to increase premiums on certain policies issued by qualified health plans under the ACA. Further, on June 14, 2018, U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in ACA risk corridor payments to third-party payors who argued were owed to them. The effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business, are not yet known.

In addition, the Centers for Medicare & Medicaid Services, or CMS, has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. On November 30, 2018, CMS announced a proposed rule that would amend the Medicare Advantage and Medicare Part D prescription drug benefit regulations to reduce out of pocket costs for plan enrollees and allow Medicare plans to negotiate lower rates for certain drugs. Among other things, the proposed rule changes would allow Medicare Advantage plans to use pre authorization (PA) and step therapy (ST) for six protected classes of drugs, with certain exceptions, permit plans to implement PA and ST in Medicare Part B drugs; and change the definition of "negotiated prices" while a definition of "price concession" in the regulations. It is unclear whether these proposed changes we be accepted, and if so, what effect such changes will have on our business. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results. We continue to evaluate the effect that the ACA and its possible repeal and replacement has on our business.

While Congress has not passed comprehensive repeal legislation, it has enacted laws that modify certain provisions of the ACA. For example, with enactment of the Tax Cuts and Jobs Act of 2017 or TCJA, which was signed by the President on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise.

On December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and inseverable feature of the ACA, and therefore because the mandate was repealed as part of the TCJA, the remaining provisions of the ACA are invalid as well. The Trump Administration and CMS have both stated that the ruling will have no immediate effect, and on December 30, 2018 the same judge issued an order staying the judgment pending appeal. The Trump Administration thereafter represented to the Court of Appeals considering this judgment that it does not oppose the lower court's ruling. On July 10, 2019, the Court of Appeals for the Fifth Circuit heard oral argument in this case. In those arguments, the Trump Administration argued in support of upholding the lower court decision. On December 18, 2019, that court affirmed the lower court's ruling that the individual mandate portion of the ACA is unconstitutional and remanded the case to the district court for reconsideration of the severability question and additional analysis of the provisions of the ACA. On January 21, 2020, the U.S. Supreme Court declined to review this decision on an expedited basis. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

We expect that these healthcare reforms, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and additional downward pressure on the price that we receive for any approved product and/or the level of reimbursement physicians receive for administering any approved product we might bring to market. Reductions in reimbursement levels may negatively impact the prices we receive or the frequency with which our products are prescribed or administered. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors.

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

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

Specifically, there have been several recent U.S. congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, Congress and the current administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. For example, on May 11, 2018, the current administration issued a plan to lower drug prices. Under this blueprint for action, the current administration indicated that the Department of Health and Human Services, or HHS, will take steps to end the gaming of regulatory and patent processes by drug makers to unfairly protect monopolies, advance biosimilars and generics to boost price competition, evaluate the inclusion of prices in drug makers' ads to enhance price competition, speed access to and lower the cost of new drugs by clarifying policies for sharing information between insurers and drug makers, avoid excessive pricing by relying more on value-based pricing by expanding outcome-based payments in Medicare and Medicaid, work to give Medicare Part D plan sponsors more negotiation power with drug makers, examine which Medicare Part B drug prices could be negotiated by Medicare Part D plans, improve the design of the Medicare Part B Competitive Acquisition Program, update Medicare's drug-pricing dashboard to increase transparency, prohibit Medicare Part D contracts that include "gag rules" that prevent pharmacists from informing patients when they could pay less out-of-pocket by not using insurance, and require that Medicare Part D plan members be provided with an annual statement of plan payments, out-of-pocket spending, and drug price increases. In addition, on December 23, 2019, the Trump Administration published a proposed rulemaking that, if finalized, would allow states or certain other non-federal government entities to submit importation program proposals to the FDA for review and approval. Applicants would be required to demonstrate that their importation plans pose no additional risk to public health and safety and will result in significant cost savings for consumers. At the same time, the FDA issued draft guidance that would allow manufacturers to import their own FDA-approved drugs that are authorized for sale in other countries (multi-market approved products).

At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures.

Moreover, legislative and regulatory proposals have also been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical drugs. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our drug candidates, if any, may be. In addition, increased scrutiny by the United States Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us and any collaborators to more stringent drug labeling and post-marketing testing and other requirements.

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

We are subject to the U.S. Foreign Corrupt Practices Act of 1977, as amended, the U.S. domestic bribery statute contained in 18 U.S.C. § 201, the U.S. Travel Act, the USA PATRIOT Act, and possibly other state and national anti-bribery and anti-money laundering laws in countries in which we conduct activities. Anti-corruption laws are interpreted broadly and prohibit companies and their employees, agents, third-party intermediaries, joint venture partners and collaborators from authorizing, promising, offering, or providing, directly or indirectly, improper payments or benefits to recipients in the public or private sector. We may have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. In addition, we may engage third party intermediaries to promote our clinical research activities abroad and/or to obtain necessary permits, licenses, and other regulatory approvals. We can be held liable for the corrupt or other illegal activities of these third-party intermediaries, our employees, representatives, contractors, partners, and agents, even if we do not explicitly authorize or have actual knowledge of such activities.

Noncompliance with anti-corruption and anti-money laundering laws could subject us to whistleblower complaints, investigations, sanctions, settlements, prosecution, other enforcement actions, disgorgement of profits, significant fines, damages, other civil and criminal penalties or injunctions, suspension and/or debarment from contracting with certain persons, the loss of export privileges, reputational harm, adverse media coverage, and other collateral consequences. If any subpoenas, investigations, or other enforcement actions are launched, or governmental or other sanctions are imposed, or if we do not prevail in any possible civil or criminal litigation, our business, results of operations and financial condition could be materially harmed. In addition, responding to any action will likely result in a materially significant diversion of management's attention

and resources and significant defense and compliance costs and other professional fees. In certain cases, enforcement authorities may even cause us to appoint an independent compliance monitor which can result in added costs and administrative burdens.

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

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological and radioactive materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties.

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

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

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

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

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

Risks Related to Employee Matters and Managing Growth

Our future success depends on our ability to retain our key executives and scientific leadership and to attract, retain and motivate qualified personnel.

We are highly dependent on the principal members of our management and scientific teams, each of whom is employed "at will," meaning we or they may terminate the employment relationship at any time. We do not maintain "key person" insurance for any of our executives or other employees. The loss of the services of any of these persons could impede the achievement of our research, development and commercialization objectives.

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

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

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

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

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

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

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

Risks Related to Our Common Stock and Other Matters

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

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

- establish a classified board of directors such that not all members of the board are elected at one time;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from the board;
- establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;

- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call stockholder meetings;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a shareholder rights plan, or so-called "poison pill," that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least 75% of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws.

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

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

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

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

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

The price of our common stock is likely to be volatile, which could result in substantial losses for purchasers of our common stock.

The trading price of our common stock has been, and may continue to be, volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. For example, since January 1, 2015 the price of our common stock on the Nasdaq Global Select Market has ranged from $28.36 per share to $138.85 per share. The stock market in general and the market for biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. The market price for our common stock may be influenced by many factors, including:

- regulatory actions with respect to our product candidates or our competitors' products and product candidates;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures, collaborations or capital commitments;
- the timing and results of clinical trials of product candidates;
- commencement or termination of collaborations for our development programs;
- failure or discontinuation of any of our development programs;
- results of clinical trials of product candidates of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- the results of our efforts to develop additional product candidates or products;
- actual or anticipated changes in estimates as to financial results or development timelines;
- announcement or expectation of additional financing efforts;
- sales of our common stock by us, our insiders or other stockholders;
- variations in our financial results, including fluctuations in levels of sales of TIBSOVO® or royalties on sales of IDHIFA®, or results of companies that are perceived to be similar to us;
- changes in estimates or recommendations by securities analysts, if any, that cover our stock;

- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this "Risk Factors" section.

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

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

Certain stockholders hold a substantial number of shares of our common stock. If such stockholders sell, or indicate an intention to sell, substantial amounts of our common stock in the public market, the trading price of our common stock could decline.

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

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

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

As of December 31, 2019, our executive officers, directors and a small group of stockholders, in the aggregate, beneficially owned shares representing a significant percentage of our capital stock. As a result, if these stockholders were to choose to act together, they would be able to significantly influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, could significantly influence the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of voting power could delay or prevent an acquisition of our company on terms that other stockholders may desire.

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

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

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

Under Section 382 of the Internal Revenue Code of 1986, as amended, if a company undergoes an "ownership change," generally defined as a greater than 50% change (by value) in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes (such as research tax credits) to offset its post-change taxable income or taxes may be limited. Our prior equity offerings and other changes in our stock ownership, some of which are outside of our control, may have resulted or could in the future result in an ownership change. We completed a review of our changes in ownership through December 31, 2019, and determined that we did not have a qualified ownership change since our last review as of December 31, 2018. We do not expect that this or any previous changes of ownership will result in our net operating loss carryforwards or certain other tax attributes expiring unutilized. Future ownership changes under Section 382 may limit the amount of net operating loss and tax credit carryforwards that we could potentially utilize to reduce future tax liabilities.

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

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

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

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

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

We have incurred and will continue to incur significant legal, accounting and other expenses as a public company. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of The Nasdaq Global Select Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations. Our management and other personnel devote, and will need to continue to devote, a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations increase our legal and financial compliance costs and make some activities more time-consuming and costly.

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

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

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

We currently lease approximately 146,000 square feet at 88 Sidney Street, 43,000 square feet at 64 Sidney Street, and 13,000 square feet at 38 Sidney Street, Cambridge, Massachusetts. All leases, as amended, expire on February 29, 2028. At the end of the initial lease period, we have the option to extend the leases at all facilities for two consecutive five year periods at the fair market rent at the time of the extension.

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

Item 3. Legal Proceedings

As of December 31, 2019, we were not a party to any material legal or arbitration proceedings. No governmental proceedings are pending or, to our knowledge, contemplated against us. We are not a party to any material proceedings in which any director, member of senior management or affiliate of ours is either a party adverse to us or our subsidiaries or has a material interest adverse to us or our subsidiaries.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

Market Information

Our common stock has been publicly traded on the Nasdaq Global Select Market under the symbol "AGIO" since July 24, 2013. Prior to that time, there was no public market for our common stock.

Holders

As of February 13, 2020, there were approximately 16 holders of record of our common stock. This number does not include beneficial owners whose shares are held by nominees in street name.

Dividends

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

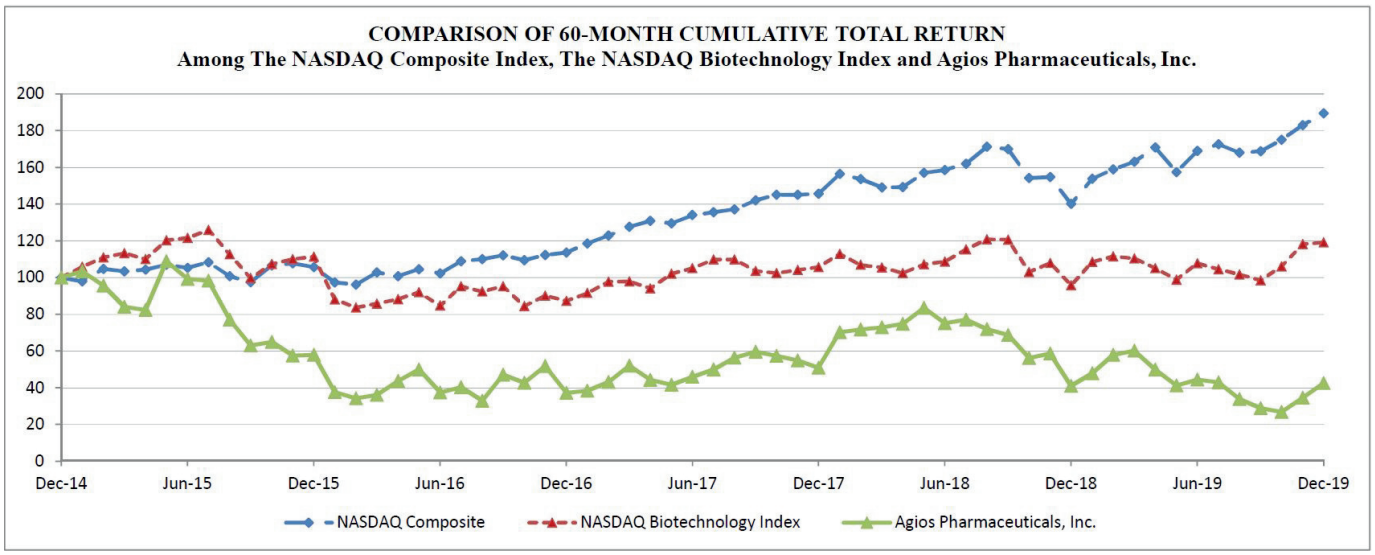
Securities Authorized for Issuance under Equity Compensation Plans

Information about our equity compensation plans is incorporated herein by reference to Item 12, *Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters*, of this Annual Report on Form 10-K.

Performance Graph

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

The following graph compares the performance of our common stock to the NASDAQ Composite Index and the NASDAQ Biotechnology Index from December 31, 2014 through December 31, 2019. The comparison assumes $100 was invested after the market closed on December 31, 2014 in our common stock and in each of the foregoing indices, and it assumes reinvestment of dividends, if any. The stock price performance included in this graph is not necessarily indicative of future stock price performance.



Recent Sales of Unregistered Securities

None.

Purchases of Equity Securities by the Issuer or Affiliated Purchasers

Neither we nor any affiliated purchaser or anyone acting on behalf of us or an affiliated purchaser made any repurchases of shares of our common stock during the fourth quarter of 2019.

Item 6. Selected Consolidated Financial Data

You should read the following selected historical consolidated financial data along with Item 7, *Management's Discussion and Analysis of Financial Condition and Results of Operations,* and the consolidated financial statements and related notes thereto contained in this Annual Report on Form 10-K. The following selected financial information included in the tables below are derived from our consolidated financial statements. Our historical results for any prior period are not necessarily indicative of results to be expected in any future period.

Selected Consolidated Financial Data

	Years Ended December 31,				
(in thousands, except shares and per share amounts)	2019	2018	2017 [1]	2016 [1]	2015 [1]
Results of Operations					
Total revenue	$ 117,912	$ 94,387	$ 43,011	$ 69,892	$ 59,119
Total cost and expenses [3]	544,245	456,866	363,805	270,877	177,819
Loss from operations	(426,333)	(362,479)	(320,794)	(200,985)	(118,700)
Net loss	$ (411,472)	$ (346,028)	$ (314,670)	$ (198,471)	$ (117,732)
Net loss per share – basic and diluted	$ (6.86)	$ (6.03)	$ (6.75)	$ (5.07)	$ (3.15)
Weighted-average number of common shares used in computing net loss per share – basic and diluted	59,994,539	57,418,300	46,587,631	39,126,400	37,429,262
Financial Position at Year End:					
Cash, cash equivalents and marketable securities	$ 717,806	$ 805,421	$ 567,750	$ 573,564	$ 375,907
Operating lease assets [2]	93,643	—	—	—	—
Total assets [2]	890,741	858,457	614,397	619,094	420,065
Deferred revenue	61,513	92,519	163,640	190,210	24,364
Operating lease liabilities [2]	112,716	—	—	—	—
Total liabilities [2]	250,213	170,920	238,894	260,503	74,947
Total stockholders' equity [2]	$ 640,528	$ 687,537	$ 375,503	$ 358,591	$ 345,118

(1) Amounts prior to 2018 do not reflect the impact of the adoption of Accounting Standards Update (ASU) 2014-09, Revenue from Contracts with Customers (Topic 606), in the first quarter of 2018 under the modified retrospective method. See Note 2. *Summary of Significant Accounting Policies* to the consolidated financial statements in this Annual Report on 10-K for additional information.

(2) Amounts prior to 2019 do not reflect the impact of the adoption of Accounting Standards Update (ASU) 2016-02, Leases (Topic 842), in the first quarter of 2019 under the optional transition method. See Note 2. *Summary of Significant Accounting Policies* to the consolidated financial statements in this Annual Report on 10-K for additional information.

(3) Expense is net of $7,811, $19,714, and $25,713 of cost reimbursement from related party for the years ended December 31, 2017, 2016 and 2015, respectively.

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

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and the related notes and other financial information included elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. You should review "Item 1A, Risk Factors" of this Annual Report on Form 10-K for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Overview

We are a biopharmaceutical company committed to the fundamental transformation of patients' lives through scientific leadership in the field of cellular metabolism and adjacent areas of biology, with the goal of creating differentiated, small molecule medicines for patients in the areas of hematologic malignancies, solid tumors and rare genetic diseases, or RGDs. To address these focus areas, 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.

Our wholly-owned product, TIBSOVO® (ivosidenib) is an oral targeted inhibitor of the mutated isocitrate dehydrogenase 1, or IDH1 enzyme. TIBSOVO® is the first and only U.S. Food and Drug Administration, or FDA-approved therapy for the treatment of adult patients with (i) relapsed or refractory acute myeloid leukemia, or R/R AML, with a susceptible IDH1 mutation as detected by an FDA-approved test (approved by the FDA in July 2018) and (ii) newly diagnosed AML with a susceptible IDH1 mutation as detected by an FDA-approved test who are at least 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy (approved by the FDA in May 2019). In December 2018, we submitted an Marketing Authorization Application, or MAA, to the European Medicines Agency, or EMA, for TIBSOVO® for the treatment of adult patients with R/R AML with an IDH1 mutation. In addition, we are currently evaluating ivosidenib in the clinical trials described below.

Our other marketed product is IDHIFA® (enasidenib), an oral targeted inhibitor of the mutated isocitrate dehydrogenase 2, or IDH2 enzyme and the first and only FDA-approved therapy for patients with R/R AML and an IDH2 mutation. 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. 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. In June 2018, Celgene submitted an MAA to the EMA for IDHIFA® for IDH2 mutant-positive AML which it subsequently withdrew in December 2019. 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-270, and AG-636.

Vorasidenib is an orally available, selective brain-penetrant pan-IDH mutant inhibitor. We are developing vorasidenib for the treatment of IDH mutant-positive low grade glioma and are currently evaluating vorasidenib in the clinical trials described below.

AG-270 is an orally available selective potent inhibitor of methionine adenosyltransferase 2a, or MAT2A. We are currently evaluating AG-270 in a phase 1 dose-escalation and expansion trial in multiple tumor types carrying a methylthioadenosine phosphorylase, or MTAP, deletion, described below.

AG-636 is an inhibitor of the metabolic enzyme dihydroorotate dehydrogenase, or DHODH. We are currently evaluating AG-636 in the phase 1 dose-escalation trial in lymphoma described below.

The lead product candidate in our RGD portfolio, mitapivat, is an activator of both wild-type and mutant pyruvate kinase-R for the potential treatment of hemolytic anemias. We are currently evaluating mitapivat for the treatment of pyruvate kinase, or PK, deficiency, thalassemia and sickle cell disease, or SCD, in the clinical trials described below.

In addition to the aforementioned development programs, we are seeking to advance a number of early-stage discovery programs in our focus areas of malignant hematology, solid tumors and RGDs based on our scientific leadership in the field of cellular metabolism and adjacent areas of biology.

Collaboration and License Agreements

Celgene Corporation

To date, our revenue has primarily been generated from our collaboration agreements with Celgene, or collectively, the Collaboration Agreements. Celgene is a related party through ownership of our common stock. In April 2010, we entered into a

discovery and development collaboration and license agreement focused on cancer metabolism, or the 2010 Agreement. The 2010 Agreement was amended in October 2011 and July 2014. In April 2015, we entered into a joint worldwide development and profit share collaboration and license agreement with Celgene, and our wholly owned subsidiary, Agios International Sarl, entered into a collaboration and license agreement with Celgene International II Sarl, or collectively, the AG-881 Agreements, to establish a worldwide collaboration focused on the development and commercialization of vorasidenib products. The AG-881 Agreements were terminated effective September 4, 2018. In May 2016, we entered into a master research and collaboration agreement with Celgene, or the 2016 Agreement. Refer to Item 1, *Business*, and Note 11. *Collaboration and License Agreements*, to the consolidated financial statements in this Annual Report on Form 10-K for additional discussion of the Collaboration Agreements.

CStone Agreement

In June 2018, we entered into an exclusive license agreement with CStone Pharmaceuticals, or 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 added by us in our sole discretion. We retain development and commercialization rights for the rest of the world. Refer to Item 1, *Business* and Note 11. *Collaboration and License Agreements*, to the consolidated financial statements in this Annual Report on Form 10-K for additional discussion of the CStone Agreement.

Financial Operations Overview

General

Since inception, our operations have primarily focused on organizing and staffing our company, business planning, raising capital, assembling our core capabilities in cellular metabolism, identifying potential product candidates, undertaking preclinical studies, conducting clinical trials and marketing our approved products. To date, we have financed our operations primarily through funding received from our various collaboration agreements discussed above, private placements of our preferred stock, our initial public offering of our common stock and concurrent private placement of common stock to an affiliate of Celgene, and our follow-on public offerings.

Additionally, since inception, we have incurred significant operating losses. Our net losses were $411.5 million, $346.0 million and $314.7 million for the years ended December 31, 2019, 2018 and 2017, respectively. As of December 31, 2019, we had an accumulated deficit of $1,516.1 million. We expect to continue to incur significant expenses and net losses until such time we are able to report profitable results. Our net losses may fluctuate significantly from year to year. We anticipate that our expenses will increase significantly as we continue to advance and expand clinical development activities for our lead programs: ivosidenib, enasidenib, vorasidenib, mitapivat, AG-270, and AG-636; continue to discover and validate novel targets and drug product candidates; expand and protect our intellectual property portfolio; and hire additional commercial, development and scientific personnel.

Revenue

Our wholly owned product, TIBSOVO®, received approval from the FDA on July 20, 2018 for the treatment of adult patients with R/R AML with susceptible IDH1 mutation. Upon FDA approval of TIBSOVO® in the U.S., we began generating product revenue from sales of TIBSOVO®. We sell TIBSOVO® to a limited number of specialty distributors and specialty pharmacy providers in the U.S., or collectively, the Customers. These Customers subsequently resell TIBSOVO® to pharmacies or dispense directly to patients. In addition to distribution agreements with Customers, we enter into arrangements with healthcare providers and payors that provide for government-mandated and/or privately-negotiated rebates, chargebacks and discounts with respect to the purchase of TIBSOVO®. For further discussion of our revenue recognition policy, see Note 2, *Summary of Significant Accounting Polices* and Note 10, *Product Revenue*, to the consolidated financial statements in this Annual Report on Form 10-K.

We also recognize collaboration revenue from our agreements with Celgene and CStone, and royalty revenue from Celgene on sales of IDHIFA®.

In the future, we expect to continue to generate revenue from a combination of product sales, royalties on product sales, cost reimbursements, milestone payments, and upfront payments to the extent we enter into future collaborations or licensing agreements.

Cost of Sales

Cost of sales consists primarily of manufacturing costs for sales of TIBSOVO®. Based on our policy to expense costs associated with the manufacturing of our products prior to regulatory approval, certain of the manufacturing costs associated with product shipments of TIBSOVO® recorded during the years ended December 31, 2019 and December 31, 2018,

respectively, were expensed prior to July 20, 2018 and, therefore, are not included in costs of sales during the years ended December 31, 2019 or 2018, respectively.

Research and development expenses

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect research and development costs to increase significantly for the foreseeable future as our product candidate development programs progress. However, the successful development of our product candidates is highly uncertain. As such, at this time, we cannot reasonably estimate or know the nature, timing and estimated costs of the efforts that will be necessary to complete the remainder of the development and commercialize these product candidates. We are also unable to positively predict when future net cash inflows will commence from TIBSOVO® (ivosidenib), IDHIFA® (enasidenib), vorasidenib, mitapivat, AG-270, AG-636, or any of our other product candidates. This is due to the numerous risks and uncertainties associated with developing medicines, including the uncertainty of:

- establishing an appropriate safety profile with an investigational new drug application, or IND, and/or new drug application, or NDA, enabling toxicology and clinical studies;
- the successful enrollment in, and completion of, clinical trials;
- the receipt of marketing approvals from applicable regulatory authorities;
- establishing compliant commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- obtaining and maintaining patent and trade secret protection and regulatory exclusivity for our product candidates;
- launching commercial sales of the products, if and when approved, whether alone or in collaboration with others; and
- maintaining an acceptable safety profile of the products following approval.

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

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

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

The following summarizes our most advanced programs:

Ivosidenib (mutant IDH1 inhibitor)

Ivosidenib is an orally available, selective, potent inhibitor of the mutated IDH1 protein, making it a highly targeted therapy 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 above. 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, MDS, cholangiocarcinoma and low grade 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. In May 2019, the FDA approved our sNDA to update the U.S. Prescribing Information for TIBSOVO® to include patients with newly diagnosed AML with a susceptible IDH1 mutation as detected by an FDA-approved test who are at least 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy. The FDA granted orphan drug designation for ivosidenib for the treatment of cholangiocarcinoma, granted Breakthrough Therapy designation for ivosidenib in combination with azacitidine for the treatment of newly diagnosed AML with an IDH1 mutation in adult patients who are at least 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy, and granted Breakthrough Therapy designation

for ivosidenib for the treatment of adult patients with relapsed or refractory MDS with a susceptible IDH1 mutation as detected by an FDA-approved test.

We are evaluating ivosidenib in the following clinical trials:

Hematologic Malignancies

- A phase 1b, multicenter, international, open-label clinical trial, to evaluate 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. This trial has completed enrollment.
- A phase 1/2 frontline combination clinical trial, conducted by Celgene, of either ivosidenib or enasidenib in combination with VIDAZA® (azacitidine) in newly diagnosed AML patients not eligible for intensive chemotherapy. The trial has completed enrollment.
- 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.
- HO150/AMLSG29, an intergroup sponsored, global, registration-enabling phase 3 trial, supported in collaboration with Celgene, combining ivosidenib or enasidenib with standard induction and consolidation chemotherapy in frontline AML patients with an IDH1 or IDH2 mutation. The trial is currently enrolling patients.
- A phase 1 multicenter, open-label, dose-escalation and expansion clinical trial, designed to assess its safety, clinical activity and tolerability as a single agent in patients with advanced hematologic malignancies with an IDH1 mutation. The trial recently reopened enrollment of its relapsed or refractory MDS arm, for which we expect to complete enrollment in 2020.

Solid Tumors

- 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. The trial has completed enrollment.
- 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 primary endpoint of the trial was met and we expect to file an sNDA with the FDA for TIBSOVO® in cholangiocarcinoma by year-end 2020.

Enasidenib (mutant IDH2 inhibitor)

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, which it subsequently withdrew in December 2019.

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 has completed enrollment.

Vorasidenib: brain penetrant pan-IDH program

Vorasidenib is an orally available, selective, brain-penetrant, pan-IDH mutant inhibitor. In connection with the termination of the AG-881 Agreements discussed above, Celgene is eligible to receive royalties from us at a low single-digit percentage rate on worldwide net sales of products containing vorasidenib.

We are evaluating vorasidenib in the following clinical trials:

- A phase 1 multi-center, open-label clinical trial of vorasidenib in patients with advanced IDH1 or IDH2 mutant-positive solid tumors, including glioma. The trial has completed enrollment.
- A perioperative study with ivosidenib and vorasidenib in low grade glioma to further investigate their effects on brain tumor tissue. The trial has completed enrollment.
- INDIGO, a registration-enabling phase 3 clinical trial of vorasidenib in low-grade (grade 2) glioma with an IDH1 or IDH 2 mutation. The trial is enrolling patients.

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 adenosine triphosphate, or 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 the study of enzyme activation in healthy volunteers, providing an opportunity to understand the safety, dosing and pharmacodynamic activity of mitapivat prior to entering a proof-of-concept study in patients. The FDA granted orphan drug designation for mitapivat for treatment of patients with PK deficiency and granted us fast track designation to mitapivat for the treatment of patients with PK deficiency.

We are evaluating mitapivat in the following clinical trials:

- 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. This trial has completed enrollment.
- ACTIVATE-T, a single arm, global, pivotal trial of mitapivat in up to 40 regularly-transfused patients with PK deficiency. The trial has completed enrollment.
- 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 trial has closed enrollment.
- A phase 2, open-label safety and efficacy clinical trial of mitapivat in approximately 20 adult patients with non-transfusion-dependent thalassemia. The trial is currently enrolling patients.
- In addition, in collaboration with the National Institutes of Health, or NIH, we are evaluating mitapivat in patients with SCD pursuant to a cooperative research and development agreement.

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.

We are evaluating AG-270 in a phase 1 trial in multiple tumor types carrying an MTAP deletion. The first part of the trial, which is complete, is a single agent dose-escalation phase in which cohorts of patients received ascending doses of AG-270 to determine the pharmacokinetics, pharmacodynamics and optimal dose, and schedule. The next phase of development, which was initiated in September 2019, is evaluating AG-270 in combination with taxanes in two areas of high unmet needs. One arm of the study will test AG-270 in combination with docetaxel in MTAP-deleted non-small cell lung cancer and the other arm will test AG-270 in combination with nab-paclitaxel and gemcitabine in MTAP-deleted pancreatic ductal adenocarcinoma. Both combination arms have initiated and are enrolling patients.

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

We have discovered a lineage-specific dependence on DHODH in hematologic malignancies, particularly AML and diffuse large B-cell lymphoma. DHODH catalyzes a critical step in the biosynthesis of pyridimidines, which are critical for the production of RNA and DNA. We believe that DHODH inhibition will be differentiated from standard-of-care therapies, both by exhibiting activity in cancers that are resistant to standard-of-care chemotherapeutics and through a mechanism of anti-tumor effect that combines cell growth arrest and cellular differentiation.

We are evaluating AG-636, an inhibitor of DHODH, licensed to us from Aurigene Discovery Technologies Limited in a phase 1 dose-escalation trial in subjects with advanced lymphomas. This trial is currently enrolling patients.

Other research and platform programs

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

Selling, general and administrative expenses

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

We anticipate that our selling, general and administrative expenses will increase in the future to support continued research and development, and commercialization activities, including the potential commercialization of our product candidates. These increases will likely include increased costs related to the hiring of additional personnel and fees to outside consultants, lawyers and accountants, among other expenses.

Critical Accounting Policies and Significant Judgments and Estimates

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

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

Revenue Recognition

We adopted Accounting Standards Codification 606, *Revenue from Contracts with Customers*, or ASC 606, effective January 1, 2018 using the modified retrospective method applied to those contracts which were not completed as of January 1, 2018. Results for reporting periods beginning after January 1, 2018 are presented under ASC 606, while prior period amounts are not adjusted and continue to be reported in accordance with our historic accounting under Accounting Standards Codification 605, *Revenue Recognition*, or ASC 605.

We applied the practical expedient that permits aggregating the effect of all contract modifications that occurred prior to January 1, 2018. No other practical expedients were used.

Under ASC 606, revenue is recognized when the customer obtains control of promised goods or services, in an amount that reflects the consideration that we expect to receive in exchange for those goods or services. To determine revenue recognition for arrangements that have been determined to be within the scope of ASC 606, we perform the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) we satisfy a performance obligation. We only apply the five-step model to contracts when it is probable that we will collect the consideration we are entitled to in exchange for the goods or services we transfer to the customer.

This new revenue standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, collaboration arrangements and financial instruments.

Once the contract is determined to be within the scope of ASC 606, we assess the goods or services promised within each contract and determine those that are performance obligations, and assess whether each promised good or service is distinct. We will then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

Product Revenue

We generate product revenue from sales of TIBSOVO® to a limited number of specialty distributors and specialty pharmacy providers in the U.S., or collectively, the Customers. The Customers subsequently resell TIBSOVO® to pharmacies or dispense directly to patients. In addition to distribution agreements with Customers, we enter into arrangements with healthcare providers and payors that provide for government-mandated and/or privately-negotiated rebates, chargebacks and discounts with respect to the purchase of TIBSOVO®.

The performance obligation related to the sale of TIBSOVO® is satisfied and revenue is recognized when the Customer obtains control of the product, which occurs at a point in time, typically upon delivery to the Customer.

Revenues from product sales are recorded at the net sales price, or transaction price, which includes estimates of variable consideration for which reserves are established and result from contractual adjustments, government rebates, returns and other allowances that are offered within the contracts with our Customers, healthcare providers, payors and other indirect customers relating to the sale of our products.

Contractual Adjustments. We generally provide Customers with discounts, including prompt pay discounts, and allowances that are explicitly stated in the contracts and are recorded as a reduction of revenue in the period the related product revenue is recognized.

Chargebacks and discounts represent the estimated obligations resulting from contractual commitments to sell products to qualified healthcare providers at prices lower than the list prices charged to Customers who directly purchase the product from us. Customers charge us for the difference between what they pay for the product and the ultimate selling price to the qualified healthcare providers. These reserves are estimated using the expected value method, based upon a range of possible outcomes that are probability-weighted for the estimated channel mix and are established in the same period that the related revenue is recognized, resulting in a reduction of product revenue.

Government Rebates. Government rebates consist of Medicare, TriCare, and Medicaid rebates, which we estimate using the expected value method, based upon a range of possible outcomes that are probability-weighted for the estimated payor mix. These reserves are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue. For Medicare, we also estimate the number of patients in the prescription drug coverage gap for whom we will owe an additional liability under the Medicare Part D program.

Returns. We estimate the amount of product sales that may be returned by Customers and record this estimate as a reduction of revenue in the period the related product revenue is recognized. We currently estimate product return liabilities using the expected value method, based on available industry data, including our visibility into the inventory remaining in the distribution channel.

Collaboration Revenue

We apply the provisions of ASC 808, *Collaborative Arrangements,* when accounting for our collaboration agreements. We evaluate the presentation of amounts due from our collaborative partners associated with activities in the collaborative arrangement based on the nature of each activity. For transactions with customers, we have reported revenues and costs in accordance with ASC 606, *Revenue from Contracts with Customers*, ASC 606-10-55-36 through 55-40, *Principal versus Agent Considerations*. We recognize revenue when the customer obtains control of promised goods or services, in an amount that reflects the consideration that we expect to receive in exchange for those goods or services. To determine revenue recognition for arrangements that have been determined to be within the scope of ASC 606, we perform the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract based on the relative standalone selling prices of the goods or services provided; and (v) recognize revenue when (or as) we satisfy a performance obligation. We only apply the five-step model to contracts when it is probable that we will collect the consideration we are entitled to in exchange for the goods or services we transfer to the customer.

Once the contract is determined to be within the scope of ASC 606, we assess the goods or services promised within each contract and determine those that are performance obligations, and assess whether each promised good or service is distinct. We will then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

The transaction price for each collaboration agreement is determined based on the amount of consideration we expect to be entitled to for satisfying all performance obligations within the agreement. Significant judgment may be required in determining the amount of variable consideration to be included in the transaction price. We use the most likely amount and expected value methods to determine variable consideration and will re-evaluate the transaction price in each reporting period and as uncertain events are resolved or other changes in circumstances occur.

As part of the initial accounting for these arrangements, we must develop assumptions that require judgment to determine the standalone selling price, or SSP, for each performance obligation identified in the contract. We use these key assumptions to determine the SSP, which include forecast of revenues, development timelines, reimbursement rates for personnel costs, discount rates and probabilities of technical and regulatory success.

We recognize the transaction price allocated to upfront license payments as revenue upon delivery of the license to the customer and resulting ability of the customer to use and benefit from the license, if the license is determined to be distinct from the other performance obligations identified in the contract. If the license is not considered to be distinct from the other performance obligations, we exercise judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied (i) at a point in time, but only for licenses determined to be distinct from other performance obligations in the contract, or (ii) over time; and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from license payments. We evaluate the measure of progress each reporting period and, if necessary, adjust the measure of performance and related revenue recognition.

A significant portion of revenue generated from our collaboration agreements with Celgene relates to the provision of research and development services whereby revenue is recognized under an input method using the ratio of effort incurred to date

compared to the total estimated effort required to complete the performance obligation. The calculation of the total estimated effort includes the total amount of forecasted costs associated with the completion of discovery, pre-clinical or clinical trials, as well as the assumed timing of these activities and estimated patient populations. Such cost estimates include forecasted direct labor and material costs, subcontractor costs, and external contract research organization costs.

Milestone Revenue (variable consideration)

Many of our collaboration agreements also entitle us to additional payments upon the achievement of performance-based milestones. These milestones are generally categorized into three types: development milestones, which are generally based on the initiation of clinical trials; regulatory milestones, which are generally based on the submission, filing or approval of regulatory applications such as an NDA in the U.S.; and sales-based milestones, which are generally based on meeting specific thresholds of sales in certain geographic areas during a specified period. Upfront and ongoing development milestones that we receive pursuant to our collaboration agreements are not subject to refund if the development activities are not ultimately successful.

For each collaboration agreement that provides for development milestone payments, we evaluate whether it is probable that the consideration associated with each milestone will not be subject to a significant reversal in the cumulative amount of revenue recognized. Amounts that meet this threshold are included in the transaction price using the most likely amount method, whereas amounts that do not meet this threshold are considered constrained and excluded from the transaction price until they meet this threshold. Milestones tied to regulatory approval, and therefore not within our control, are considered constrained until such approval is received. At the end of each subsequent reporting period, we re-evaluate the probability of a significant reversal of the cumulative revenue recognized for our milestones, and, if necessary, adjust our estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues from collaborators and loss in the period of adjustment. For arrangements that include sales-based milestone or royalty payments based on the level of sales, and in which the license is deemed to be the predominant item to which the sales-based milestone or royalties relate to, we recognize revenue in the period in which the sales-based milestone is achieved and in the period in which the sales associated with the royalty occur.

Product Revenue - Prior to ASC 606 Adoption

We did not have any product sales for the year ended December 31, 2017. Therefore, there was no impact to our revenue recognition model from the adoption of ASC 606.

Collaboration Revenue - Prior to ASC 606 Adoption

Revenue for the year ended December 31, 2017 was recognized under ASC 605. Accordingly, revenue was recognized for each unit of accounting when all of the following criteria are met: (i) persuasive evidence of an arrangement exists; (ii) delivery has occurred or services have been rendered; (iii) the seller's price to the buyer is fixed or determinable; and (iv) collectability is reasonably assured.

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

We accounted for collaboration agreements with Celgene under ASC 605-25, *Revenue Recognition — Multiple-Element Arrangements*, or ASC 605-25. The arrangement consideration was allocated to each unit of accounting based on the relative selling price, using our best estimate of selling price of each unit of accounting, if vendor specific objective evidence or third-party evidence was not available. We recognized revenue for the units of accounting as our obligation under the agreement was satisfied.

We recognize revenue for the units of accounting over the term of the related contract or as undelivered items are delivered (proportional performance method), as appropriate. Under the proportional performance method, the consideration allocated to each unit of accounting is recognized as revenue based on the ratio of the level of effort incurred to date compared to the total estimated level of effort required to complete our performance obligations under the unit of accounting. Determining the total estimated level of effort required to complete all performance obligations requires judgment and estimation, including assumptions regarding future operating performance, the timelines of the clinical trial approvals and the estimated patient populations.

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

Milestone Revenue - Prior to ASC 606 Adoption

In accordance with ASC 605-28, *Revenue Recognition — Milestone Method*, at the inception of each arrangement that included milestone payments, we evaluated each contingent payment on an individual basis to determine whether they were considered substantive milestones. This evaluation included an assessment of whether (a) the consideration was commensurate with either (1) our performance to achieve the milestone, or (2) the enhancement of the value of the delivered item(s) as a result of a specific outcome resulting from our performance to achieve the milestone, (b) the consideration related solely to past performance, and (c) the consideration was reasonable relative to all of the deliverables and payment terms within the arrangement.

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

Accrued research and development expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued expenses. This process involves reviewing quotations and contracts, identifying services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. Certain service providers invoice us in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date in our financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. Examples of estimated accrued research and development expenses include fees paid to: (i) CROs and other third parties in connection with clinical studies and preclinical development activities; (ii) investigative sites in connection with clinical studies; and (iii) third parties related to product manufacturing, development and distribution of clinical supplies.

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

Stock-based compensation

We account for stock-based compensation awards in accordance with ASC 718, *Compensation –Stock Compensation*. For stock-based awards granted to employees, non-employees and members of the board of directors for their services and for participation in our employee stock purchase plan, we estimate the grant date fair value of each option award using the Black-Scholes option-pricing model. The use of the Black-Scholes option-pricing model requires us to make assumptions with respect to the expected term of the option, the expected volatility of the common stock consistent with the expected life of the option, risk-free interest rates and expected dividend yields of the common stock.

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

Volatility. We use a weighted-average of expected volatility based on the volatilities of a representative group of publicly traded biopharmaceutical companies, including ourselves. The expected volatility has been determined using a weighted-average of the historical volatilities of the representative group of companies for a period equal to the expected term of the option grant.

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

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

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

For awards subject to service-based vesting conditions, we recognize stock-based compensation expense equal to the grant date fair value of stock options on a straight-line basis over the requisite service period. For awards subject to both performance and service-based vesting conditions, we recognize stock-based compensation expense over the remaining service period if the performance condition is considered probable of achievement using management's best estimates.

Results of Operations

Certain prior-year amounts have been reclassified to conform with current presentation.

Comparison of years ended December 31, 2019, 2018 and 2017

Total Revenue

(In thousands)	2019	2018	2017 [1]
Revenues:			
Product revenue, net	$ 59,851	$ 13,841	$ —
Collaboration revenue – related party	39,257	60,661	41,074
Collaboration revenue – other	8,262	12,670	—
Royalty revenue – related party	10,542	7,215	1,937
Total revenue	$ 117,912	$ 94,387	$ 43,011

(1) Amounts prior to 2018 do not reflect the impact of the adoption of Accounting Standards Update (ASU) 2014-09, Revenue from Contracts with Customers (Topic 606), in the first quarter of 2018 under the modified retrospective method. See Note 2. Summary of Significant Accounting Policies to the consolidated financial statements in this Annual Report on Form 10-K for additional information.

Total Revenue – 2019 vs 2018 – The increase in Total Revenue of $23.5 million in 2019 compared to 2018 was primarily due to an increase in product revenue of $46.0 million partially offset by a decrease in collaboration revenue - related party of $21.4 million. The increase in product revenue related to a full year of sales of TIBSOVO® in 2019 as compared to a partial year of sales in 2018. The decrease in collaboration revenue-related party was primarily due to the $15.0 million milestone payment related to Celgene's filing of an MAA to the EMA for IDHIFA® for IDH2 mutant-positive R/R AML in 2018.

Total Revenue – 2018 vs. 2017 – The increase in Total Revenue of $51.4 million in 2018 compared to 2017 was primarily due to $13.8 million of product revenue, $19.6 million of collaboration revenue – related party, and $12.7 million of collaboration revenue – other. The increase in product revenue related to sales of our first commercial product, TIBSOVO®, in the U.S. beginning on July 20, 2018. The increase in collaboration revenue – related party included a $15.0 million milestone payment related to Celgene's filing of an MAA to the EMA for IDHIFA® for IDH2 mutant-positive R/R AML. The increase in collaboration revenue – other was primarily due to revenue recognition under the CStone Agreement, which was entered into in 2018.

Total Operating Expenses

(In thousands)	2019	2018	2017 [1]
Cost and expenses:			
Cost of sales	$ 1,317	$ 1,397	$ —
Research and development [2]	410,894	341,324	292,681
Selling, general and administrative	132,034	114,145	71,124
Total Operating Expenses	$ 544,245	$ 456,866	$ 363,805

(1) Amounts prior to 2018 do not reflect the impact of the adoption of Accounting Standards Update (ASU) 2014-09, Revenue from Contracts with Customers (Topic 606), in the first quarter of 2018 under the modified retrospective method. See Note 2. *Summary of Significant Accounting Policies* to the consolidated financial statements in this Annual Report on Form 10-K for additional information.

(2) Total research and development expenses are net of cost reimbursements from related party of $0, $0, and $7,811 for the years ended December 31, 2019, 2018 and 2017, respectively.

Total Operating Expenses – 2019 vs 2018 – The increase in Total Operating Expenses of $87.4 million in 2019 compared to 2018 was primarily due to an increase of $69.6 million in research and development expenses, which is described below under Research and Development Expenses. In addition, we expect cost of sales to increase moderately in 2020 as we have depleted our finished goods inventory that was expensed prior to receiving FDA approval of TIBSOVO®.

Total Operating Expenses – 2018 vs. 2017 – The increase in Total Operating Expenses of $93.1 million in 2018 compared to 2017 was primarily due to an increase of $48.6 million in research and development expenses and an increase of $43.0 million in selling, general and administrative expenses. The increase in selling, general and administrative expenses was primarily due to higher expenses of $27.3 million related to supporting our commercial organization for commercialization of TIBSOVO® as

of July 20, 2018. The increase in research and development expenses was primarily due to an increase of $52.3 million in outside services; both of which include cost reimbursements recorded as a reduction of research and development expenses. See the Research and Development Expenses table below for additional details on expense drivers.

Research and Development Expenses

Our research and development expenses, by major program, are outlined in the table below:

(In thousands)	2019	2018	2017 [1]
IDH1 inhibitor (ivosidenib)	$ 79,087	$ 74,600	$ 81,640
IDH2 inhibitor (enasidenib)	3,983	4,140	3,340
Pan IDH inhibitor (vorasidenib (AG-881))	23,060	7,005	1,137
PKR activator (mitapivat)	47,481	31,254	19,445
MAT2A inhibitor (AG-270)	11,058	9,656	9,603
DHODH inhibitor (AG-636)	8,663	4,428	3,999
Other research and platform programs	44,057	36,507	17,638
Total direct research and development expenses	217,389	167,590	136,802
Compensation and related expenses	144,888	135,227	119,186
Facilities and IT related expenses & other	48,617	38,507	36,693
Total indirect research and development expenses	193,505	173,734	155,879
Total research and development expense	$ 410,894	$ 341,324	$ 292,681

(1) Total research and development expenses are net of cost reimbursements from related party of $0, $0, and $7,811 for the years ended December 31, 2019, 2018 and 2017, respectively.

Total Research and development Expenses – 2019 vs 2018 – The increase in research and development expenses of $69.6 million in 2019 compared to 2018 was primarily due to a $49.8 million increase in our direct expenses and a $19.8 million increase in our indirect expenses. The increase in direct expenses of $49.8 million was primarily due to a $16.2 million increase for mitapivat driven by continuing enrollment and ongoing trial activities for ACTIVATE, ACTIVATE-T, DRIVE PK and related rollover studies, a $16.1 million increase for vorasidenib (AG-881) driven by clinical start up activities for the phase 3 INDIGO trial including clinical diagnostic costs, and research support activities including clinical pharmacology studies, and a $7.6 million increase in other research and platform program expenses driven by our other research programs due to the ongoing progression of our product pipeline. The increase in indirect expenses of $19.8 million was primarily due to a $10.1 million increase in facility and IT related expenses primarily driven by the new leasing space that we entered into in 2019 and associated costs and a $9.7 million increase in employee related expenses driven by additional hiring during the year to support increased clinical program activity.

Total Research and development Expenses – 2018 vs. 2017 -

- Ivosidenib costs decreased compared to the prior period as prior period costs included manufacturing expenses associated with our initial commercial inventory as part of our NDA submission in December 2017.
- Enasidenib costs increased as a result of increased internal and external expenses related to our ongoing phase 1b frontline combination trial development work.
- Vorasidenib (AG-881) overall costs decreased as our phase 1 trial in patients with advanced IDH1 or IDH2 mutant-positive hematologic malignancies and our phase 1 trial in IDH1 or IDH2 mutant-positive advanced solid tumors, including glioma, both completed their dose escalation portions. Cost reimbursements for vorasidenib (AG-881) were recognized as revenue in 2018 and as a reduction of R&D expenses in 2017.
- Mitapivat costs increased as a result of the enrollment costs for the ACTIVATE-T trial, which we initiated in April 2018, and the start-up costs for the ACTIVATE trial, which we initiated in June 2018.
- AG-270 costs increased as we initiated a phase 1 trial in March 2018.
- AG-636 costs increased as we completed IND-enabling studies in anticipation of the IND filing, which occurred in October 2018. Prior year development costs for AG-636 were included in other research and platform programs.
- The increase in the costs of other research and platform programs includes activities related to exploratory efforts, target validation and lead optimization for our discovery and follow-on programs, and our proprietary metabolomics platform.

Interest Income

(In thousands)	2019	2018	2017
Interest income, net	$ 14,861	$ 16,451	$ 6,124

Interest Income – 2019 vs 2018 – The decrease in interest income in 2019 compared to 2018 is primarily driven by lower investment balances in 2019 due to lower interest earned on investments. The lower interest earned on investments in 2019 was primarily due to the amount and timing of the receipt of funds of $277.2 million in November 2019 from a follow-on common stock offering compared to $516.2 million in January 2018 from a follow-on common stock offering.

Interest Income – 2018 vs. 2017 - The increase in interest income in 2018 compared to 2017 is primarily driven by higher investment balances due to higher interest earned on investments. The higher interest earned on investments in 2018 was primary due to the amount and timing of the receipt of funds of $516.2 million in January 2018 from a follow-on common stock offering compared to $270.2 million in April 2017 from a follow-on common stock offering

Loss from Operations and Net Loss

(In thousands)	2019	2018	2017 [(1)]
Loss from operations	$ (426,333)	$ (362,479)	$ (320,794)
Net loss	(411,472)	(346,028)	(314,670)

(1) Amounts prior to 2018 do not reflect the impact of the adoption of Accounting Standards Update (ASU) 2014-09, Revenue from Contracts with Customers (Topic 606), in the first quarter of 2018 under the modified retrospective method. See Note 2. Summary of Significant Accounting Policies to the consolidated financial statements in this Annual Report on Form 10-K for additional information.

Loss from operations and net loss – 2019 vs 2018 – The increase in loss from operations and net loss in 2019 compared to 2018 is primarily driven by higher operating expenses as described above in Total Operating Expenses.

Loss from operations and net loss – 2018 vs. 2017 - The increase in loss from operations and net loss in 2018 compared to 2017 is primarily driven by higher operating expenses as described above in Total Operating Expenses.

Liquidity and Capital Resources

Sources of liquidity

Since our inception, and through December 31, 2019, we have funded our operations through upfront, milestone, extension, cost reimbursement and royalty payments related to our collaboration agreements, product sales, proceeds received from our issuance of preferred stock, our initial public offering and concurrent private placement of common stock to an affiliate of Celgene, and our follow-on public offerings.

In November 2019, we completed a public offering of 9,487,500 shares of common stock at an offering price of $31.00 per share. We received net proceeds from this offering of $277.2 million, after deducting underwriting discounts and commissions paid by us, certain of which are subject to reimbursement.

In January 2018, we completed a public offering of 8,152,986 shares of common stock at an offering price of $67.00 per share. We received net proceeds from this offering of $516.2 million, after deducting underwriting discounts and commissions paid by us.

In April 2017, we completed a public offering of 5,050,505 shares of common stock at an offering price of $49.50 per share. We received net proceeds from this offering of $235.0 million, after deducting underwriting discounts and commissions paid by us. In addition, we granted the underwriters the right to purchase up to an additional 757,575 shares of common stock, which was exercised in April 2017, resulting in additional net proceeds to us of $35.2 million, after underwriting discounts and commissions. After giving effect to the full exercise of the over-allotment option, the number of shares sold by us in the public offering totaled 5,808,080 shares, and net proceeds to us totaled $270.2 million, after underwriting discounts and commissions.

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

Cash flows

The following table provides information regarding our cash flows for the years ended December 31, 2019, 2018 and 2017:

(In thousands)	2019	2018	2017
Net cash used in operating activities	$ (370,622)	$ (304,421)	$ (285,232)
Net cash provided by (used in) investing activities	91,440	(273,825)	(57,908)
Net cash provided by financing activities	289,611	546,024	285,110
Net change in cash and cash equivalents	$ 10,429	$ (32,222)	$ (58,030)

Net cash used in operating activities

During the year ended December 31, 2019, we received $60.7 million from product sales of TIBSOVO®, $19.1 million in cost reimbursements and royalty payments under our collaboration agreement with Celgene, and a $5.0 million milestone payment under the CStone Agreement. The significant increase in product sales of TIBSOVO® was primarily due to having a full year of sales in 2019. These amounts were offset by increased operating expenses that related to increases in clinical study costs due to advancements in our most advanced product candidates, commercialization efforts, expanded facilities and increased staffing needs due to our expanding operations.

During the year ended December 31, 2018, we received $10.0 million from product sales of TIBSOVO®, $20.1 million in cost reimbursements and royalty payments and a $15.0 million milestone payment under our collaboration agreements with Celgene and $12.0 million under the CStone Agreement. These amounts were offset by increased operating expenses that related to increases in clinical study costs due to advancements in our most advanced product candidates, commercialization efforts, expanded facilities and increased staffing needs due to our expanding operations.

During the year ended December 31, 2017, we incurred increased operating expenses related to increases in clinical study costs due to advancements in our most advanced product candidates, and expanded facilities and increased staffing needs due to our expanding operations. These amounts were offset by the receipt of $17.0 million in cost reimbursements related to our collaboration agreements and $3.1 million as reimbursement of tenant improvements under our lease agreement.

Net cash provided by (used in) investing activities

The cash provided by investing activities for the year ended December 31, 2019 was primarily the result of lower purchases of marketable securities than proceeds from maturities and sales of marketable securities, offset by $12.2 million in purchases of property and equipment.

The cash used in investing activities for the year ended December 31, 2018 was primarily the result of higher purchases of marketable securities than proceeds from maturities and sales of marketable securities, and $7.0 million in purchases of property and equipment.

The cash used in investing activities for the year ended December 31, 2017 was primarily the result of higher purchases of marketable securities than proceeds from maturities and sales of marketable securities, in addition to $4.6 million for purchases of property and equipment.

Net cash provided by financing activities

The cash provided by financing activities for the year ended December 31, 2019 was primarily the result of proceeds of $277.2 million from the November 2019 follow-on public offering, net of underwriting discounts and commissions, as well as proceeds of $12.5 million received from stock option exercises and purchases made pursuant to our employee stock purchase plan.

The cash provided by financing activities for the year ended December 31, 2018 was primarily the result of proceeds of $516.2 million from the January 2018 follow-on public offering, net of underwriting discounts and commissions, as well as proceeds of $30.2 million received from stock option exercises and purchases made pursuant to our employee stock purchase plan.

The cash provided by financing activities for the year ended December 31, 2017 was primarily the result of proceeds of $270.2 million from the April 2017 follow-on public offering of our common stock, net of underwriting discounts and commissions, and proceeds of $14.2 million received from stock option exercises and purchases made pursuant to our employee stock purchase plan.

Funding requirements

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue to commercialize TIBSOVO®, and continue the research, development and clinical trials of, and seek additional marketing approvals for, our product candidates. If we obtain additional marketing approval for any of our other product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution to the extent that

such sales, marketing, manufacturing and distribution are not the responsibility of Celgene, CStone or other partners. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations.

We expect that our existing cash, cash equivalents and marketable securities as of December 31, 2019, together with anticipated product and royalty revenue, anticipated interest income and anticipated expense reimbursements under our collaboration agreements, but excluding any additional collaboration-related payments, will enable us to fund our operating expenses and capital expenditure requirements through at least the end of 2021. Our future capital requirements will depend on many factors, including:

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

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements. We do not have any committed potential external source of funds other than our collaborations. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

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

Off-Balance Sheet Arrangements

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

Contractual Obligations

The following table summarizes our significant contractual obligations as of the payment due date by period at December 31, 2019:

	Payments due by period				
(In thousands)	Total	Less than 1 year	1-3 years	3-5 years	More than 5 years
Operating lease obligations	$ 145,072	$ 13,242	$ 31,153	$ 36,786	$ 63,891
Manufacturing arrangements	5,269	1,205	4,064	—	—

We enter into agreements in the normal course of business with CROs for clinical trials and CMOs for supply manufacturing and with vendors for preclinical research studies and other services and products for operating purposes. These contractual obligations are cancelable at any time by us, generally upon prior written notice to the vendor, and are thus not included in the contractual obligations table.

Other than the specific payments noted in the table of contractual obligations, we are obligated to make future milestone and royalty payments under our global license agreement with Aurigene, or the Aurigene Agreement. Financial terms of the Aurigene Agreement include potential future milestone payments of up to $15.0 million if we achieve certain development and regulatory milestones and low single-digit royalties on net product sales, if any. During the year ended December 31, 2019,

upon initiation of the first phase 1 clinical trial for DHODH, we made a milestone payment of $2.0 million. We do not expect to make any milestone payments during the next 12 months.

In addition, we are also party to other license agreements which include contingent payments. However, contingent payments related to these license agreements are not disclosed as the satisfaction of these contingent payments is uncertain at December 31, 2019 and, if satisfied, the timing of payment for these amounts was not reasonably estimable at December 31, 2019. Commitments related to the license agreements include contingent payments that will become payable if and when certain development, regulatory and commercial milestones are achieved. During the next 12 months, we do not expect to make milestone payments related to such license agreements.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

We are exposed to market risk related to changes in interest rates. As of December 31, 2019, we had cash, cash equivalents and marketable securities of $717.8 million, consisting primarily of investments in U.S. Treasuries, certificates of deposit, and government and corporate debt securities. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because our investments are in short-term marketable securities. Our marketable securities are subject to interest rate risk and could fall in value if market interest rates increase. Due to the short-term duration of our investment portfolio and the low risk profile of our investments, we do not believe an immediate and uniform 100 basis point increase in interest rates would have a material effect on the fair market value of our investment portfolio.

We are also exposed to market risk related to changes in foreign currency exchange rates. We have contracts with CROs and CMOs that are located in Asia and Europe that are denominated in foreign currencies. We are subject to fluctuations in foreign currency rates in connection with these agreements. We do not currently hedge our foreign currency exchange rate risk. As of December 31, 2019 and December 31, 2018, we had minimal or no liabilities denominated in foreign currencies.

Item 8. Financial Statements and Supplementary Data

The financial statements required to be filed pursuant to this Item 8 are appended to this Annual Report on Form 10-K. An index of those financial statements is found in Item 15, *Exhibits and Financial Statement Schedules*, of this Annual Report on Form 10-K.

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

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our principal executive officer and our principal financial officer, evaluated, as of the end of the period covered by this Annual Report on Form 10-K, the effectiveness of our disclosure controls and procedures. Based on that evaluation of our disclosure controls and procedures as of December 31, 2019, our principal executive officer and principal financial officer concluded that our disclosure controls and procedures as of such date are effective at the reasonable assurance level. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act are recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by us in the reports we file or submit under the Exchange Act is accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and our management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

Management's Annual Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over our financial reporting. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, our principal executive and principal financial officers and effected by our board of directors, management and other personnel to provide reasonable assurance regarding the reliability of financial reporting and

the preparation of financial statements for external purposes in accordance with U.S. GAAP. Our internal control over financial reporting includes those policies and procedures that:

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

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

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2019. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in its 2013 Internal Control – Integrated Framework. Based on our assessment, our management has concluded that, as of December 31, 2019, our internal control over financial reporting is effective based on those criteria.

The effectiveness of our internal control over financial reporting as of December 31, 2019, has been audited by PricewaterhouseCoopers LLP, an independent registered public accounting firm, as stated in their report, which is included herein.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during the fiscal quarter ended December 31, 2019 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this Item 10 will be included in our definitive proxy statement to be filed with the Securities and Exchange Commission, or SEC, with respect to our 2020 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 11. Executive Compensation

The information required by this Item 11 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2020 Annual Meeting of Stockholders and is incorporated herein by reference.

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

The information required by this Item 12 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2020 Annual Meeting of Stockholders and is incorporated herein by reference.

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

The information required by this Item 13 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2020 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services

The information required by this Item 14 will be included in our definitive proxy statement to be filed with the SEC with respect to our 2020 Annual Meeting of Stockholders and is incorporated herein by reference.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(1) Financial Statements

The following documents are included on pages F-1 through F-37 attached hereto and are filed as part of this Annual Report on Form 10-K.

(2) Financial Statement Schedules

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

(3) Exhibits

		Incorporated by Reference				
Exhibit Number	Description of Exhibit	Form	File Number	Date of Filing	Exhibit Number	Filed Herewith
3.1	Restated Certificate of Incorporation of the Registrant	8-K	001-36014	July 30, 2013	3.1	
3.2	Second Amended and Restated By-Laws	8-K	001-36014	December 19, 2018	3.1	
4.1	Specimen Stock Certificate evidencing the shares of common stock	S-1	333-189216	June 24, 2013	4.1	
4.2	Second Amended and Restated Investor Rights Agreement dated as of November 16, 2011	S-1	333-189216	June 10, 2013	4.2	
4.3	Description of Securities Registered Under Section 12 of the Securities Exchange Act of 1934					X
10.1#	2007 Stock Incentive Plan	S-1	333-189216	June 10, 2013	10.1	
10.2#	Form of Incentive Stock Option Agreement under 2007 Stock Incentive Plan	S-1	333-189216	June 10, 2013	10.2	
10.3#	Form of Nonstatutory Stock Option Agreement under 2007 Stock Incentive Plan	S-1	333-189216	June 10, 2013	10.3	
10.4#	2013 Stock Incentive Plan	S-1	333-189216	June 24, 2013	10.4	
10.5#	Form of Incentive Stock Option Agreement under 2013 Stock Incentive Plan	S-1	333-189216	June 24, 2013	10.5	
10.6#	Form of Nonstatutory Stock Option Agreement under 2013 Stock Incentive Plan	S-1	333-189216	June 24, 2013	10.6	
10.7#	2013 Employee Stock Purchase Plan	S-1	333-189216	June 24, 2013	10.7	
10.8#	Letter Agreement, dated as of July 22, 2010, between the Registrant and Scott Biller, Ph.D.	S-1	333-189216	July 11, 2013	10.10	

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
10.9	Form of Indemnification Agreement between the Registrant and each of its Executive Officers and Directors	S-1	333-189216	July 11, 2013	10.12	
10.10#	Letter Agreement, dated as of April 1, 2014, between the Registrant and Christopher Bowden, Ph.D.	10-K	001-36014	February 26, 2016	10.13	
10.11†	Discovery and Development Collaboration and License Agreement, dated as of April 14, 2010, as amended on October 3, 2011, between the Registrant and Celgene Corporation	S-1	333-189216	July 16, 2013	10.14	
10.12†	Third Amendment to Discovery and Development Collaboration and License Agreement, dated July 14, 2014 between the Registrant and Celgene Corporation	10-K	001-36014	February 24, 2015	10.15	
10.13	Common Stock Purchase Agreement, dated as of July 16, 2013, between the Registrant and Celgene Alpine Investment Co., LLC	S-1	333-189216	July 16, 2013	10.15	
10.14	Lease, dated as of September 15, 2014, between the Registrant and Forest City 88 Sidney, LLC	8-K	001-36014	September 19, 2014	10.1	
10.15	First Amendment to Lease for 88 Sidney Street, dated as of November 21, 2014, between the Registrant and Forest City 88 Sidney, LLC	8-K	001-36014	November 26, 2014	10.1	
10.16#	Summary Description of Annual Cash Incentive Program	10-Q	001-36014	May 11, 2015	10.1	
10.17	Second Amendment to Lease for 88 Sidney Street, dated July 20, 2015, by and between the Registrant and Forest City 88 Sidney Street, LLC	8-K	001-36014	July 23, 2015	10.1	
10.18†	Collaboration and License Agreement by and between the Registrant and Celgene Corporation Re: AGI-23088 for the US Territory, dated as of April 27, 2015	10-Q	001-36014	August 7, 2015	10.1	
10.19†	Collaboration and License Agreement by and between Agios International Sarl and Celgene International II Sarl Re: AGI-23088 for the ROW Territory, dated as of April 27, 2015	10-Q	001-36014	August 7, 2015	10.2	
10.20#	Form of Performance Share Unit Agreement under 2013 Stock Incentive Plan	10-K	001-36014	February 26, 2016	10.25	
10.21#	Severance Benefits Plan	8-K	001-36014	April 22, 2016	10.1	
10.22†	Master Research and Collaboration Agreement, dated May 17, 2016, by and among the Registrant, Celgene Corporation and Celgene RIVOT Ltd.	10-Q	001-36014	August 8, 2016	10.1	
10.23#	Letter Agreement between the Registrant and Andrew Hirsch, effective August 11, 2016	8-K	001-36014	August 16, 2016	99.2	
10.24	Lease, dated as of November 17, 2017, between the Registrant and UP 64 Sidney Street, LLC	8-K	001-36014	November 22, 2017	10.1	

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
10.25	Third Amendment to Lease for 88 Sidney Street, dated November 17, 2017, by and between the Registrant and Forest City 88 Sidney Street, LLC	8-K	001-36014	November 22, 2017	10.2	
10.26	First Amendment of Lease, dated April 11, 2018, by and between UP 64 Sidney Street, LLC and Agios Pharmaceuticals. Inc.	8-K	001-36014	April 13, 2018	10.1	
10.27#	Form of Restricted Stock Unit Agreement under 2013 Stock Incentive Plan (for employees)	10-Q	001-36014	May 4, 2018	10.1	
10.28†	License Agreement, dated June 25, 2018, by and between Agios Pharmaceuticals, Inc. and CStone Pharmaceuticals	10-Q	001-36014	August 2, 2018	10.2	
10.29#	Amended and Restated Letter Agreement, dated as of August 30, 2018, between the Registrant and David P. Schenkein, M.D.	10-Q	001-36014	November 1, 2018	10.1	
10.30#	Letter Agreement, dated as of August 30, 2018, between the Registrant and Jacqualyn A. Fouse, Ph.D.	10-Q	001-36014	November 1, 2018	10.2	
10.31#	Form of Restricted Stock Unit Agreement under 2013 Stock Incentive Plan (for directors)	10-K	001-36014	February 14, 2019	10.32	
10.32	Lease, dated as of April 11, 2019, by and between the Registrant and Thirty-Eight Sidney Street Limited LLC	10-Q	001-36014	August 1, 2019	10.1	
10.33	Fourth Amendment to Lease, dated as of April 11, 2019, by and between the Registrant and Forest City 88 Sidney Street, LLC	10-Q	001-36014	August 1, 2019	10.2	
10.34	Third Amendment of Lease, dated as of April 11, 2019, by and between the Registrant and UP 64 Sidney Street, LLC	10-Q	001-36014	August 1, 2019	10.3	
10.35#	Letter Agreement, dated as of September 17, 2019, between the Registrant and Jonathan Biller					X
21.1	Subsidiaries of the Registrant					X
23.1	Consent of PricewaterhouseCoopers LLP, an Independent Registered Public Accounting Firm					
31.1	Certification of principal executive officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended					X
31.2	Certification of principal financial officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended.					X
32.1*	Certification of principal executive officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.					X
32.2*	Certification of principal financial officer pursuant to 18 U.S.C. §1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.					X

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
101.INS	XBRL Instance Document					X
101.SCH	XBRL Taxonomy Extension Schema Document					X
101.CAL	XBRL Taxonomy Calculation Linkbase Document					X
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document					X
101.LAB	XBRL Taxonomy Label Linkbase Document					X
101.PRE	XBRL Taxonomy Presentation Linkbase Document					X
104	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101)					X

#	Indicates management contract or compensatory plan or arrangement.
†	Confidential treatment has been granted as to certain portions, which portions have been omitted and filed separately with the Securities and Exchange Commission.
*	This certification will not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, or otherwise subject to the liability of that section. Such certification will not be deemed to be incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act, except to the extent specifically incorporated by reference into such filing.

Item 16. Form 10-K Summary

None.

SIGNATURES

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

AGIOS PHARMACEUTICALS, INC.

February 19, 2020

By: /s/ Jacqualyn A. Fouse

Jacqualyn A. Fouse, Ph.D.
Chief Executive Officer

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

Signature	Title	Date
/s/ Jacqualyn A. Fouse Jacqualyn A. Fouse, Ph.D.	Chief Executive Officer and Director (Principal executive officer)	February 19, 2020
/s/ Andrew Hirsch Andrew Hirsch	Chief Financial Officer (Principal financial officer)	February 19, 2020
/s/ Carman Alenson Carman Alenson	Vice President of Accounting, Treasury and Tax (Principal accounting officer)	February 19, 2020
/s/ Paul J. Clancy Paul J. Clancy	Director	February 19, 2020
/s/ Ian Clark Ian Clark	Director	February 19, 2020
/s/ Kaye Foster Kaye Foster	Director	February 19, 2020
/s/ Maykin Ho Maykin Ho, Ph.D.	Director	February 19, 2020
/s/ John M. Maraganore John M. Maraganore, Ph.D.	Director	February 19, 2020
/s/ David Scadden David Scadden, M.D.	Director	February 19, 2020
/s/ David P. Schenkein David P. Schenkein, M.D.	Director	February 19, 2020

Agios Pharmaceuticals, Inc.

Index to Consolidated Financial Statements

Report of Independent Registered Public Accounting Firm

To the Board of Directors and Stockholders of Agios Pharmaceuticals, Inc.

Opinions on the Financial Statements and Internal Control over Financial Reporting

We have audited the accompanying consolidated balance sheets of Agios Pharmaceuticals, Inc. and its subsidiaries (the "Company") as of December 31, 2019 and 2018, and the related consolidated statements of operations, of comprehensive loss, of stockholders' equity and of cash flows for each of the three years in the period ended December 31, 2019, including the related notes (collectively referred to as the "consolidated financial statements"). We also have audited the Company's internal control over financial reporting as of December 31, 2019, based on criteria established in *Internal Control - Integrated Framework* (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO).

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of the Company as of December 31, 2019 and 2018, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2019 in conformity with accounting principles generally accepted in the United States of America. Also in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2019, based on criteria established in *Internal Control - Integrated Framework* (2013) issued by the COSO.

Changes in Accounting Principles

As discussed in Note 2 to the consolidated financial statements, the Company changed the manner in which it accounts for leases in 2019 and the manner in which it accounts for revenue from contracts with customers in 2018.

Basis for Opinions

The Company's management is responsible for these consolidated financial statements, for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting, included in Management's Annual Report on Internal Control over Financial Reporting appearing under Item 9A. Our responsibility is to express opinions on the Company's consolidated financial statements and on the Company's internal control over financial reporting based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audits to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud, and whether effective internal control over financial reporting was maintained in all material respects.

Our audits of the consolidated financial statements included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, and testing and evaluating the design and operating effectiveness of internal control based on the assessed risk. Our audits also included performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide a reasonable basis for our opinions.

Definition and Limitations of Internal Control over Financial Reporting

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

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

Critical Audit Matters

The critical audit matter communicated below is a matter arising from the current period audit of the consolidated financial statements that was communicated or required to be communicated to the audit committee and that (i) relates to accounts or disclosures that are material to the consolidated financial statements and (ii) involved our especially challenging, subjective, or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Revenue recognition – Celgene Collaboration Agreement Research and Development Services Recognized Under an Input Method

As described in Notes 2 and 11 to the consolidated financial statements, the Company recognizes revenue arising from collaboration agreements with Celgene. A significant portion of revenue generated from the Company's collaboration agreements with Celgene relates to the provision of research and development services whereby revenue is recognized under an input method using the ratio of effort incurred to date compared to the total estimated effort required to complete the performance obligation. The calculation of the total estimated effort includes the total amount of forecasted costs associated with the completion of discovery, pre-clinical or clinical trials, as well as the assumed timing of these activities and estimated patient populations. Such cost estimates include forecasted direct labor and material costs, subcontractor costs, and external contract research organization costs. Research and development services revenue recognized from the collaboration with Celgene were $36.0 million during the year-ended December 31, 2019.

The principal considerations for our determination that performing procedures relating to revenue recognition – Celgene collaboration agreement research and development services recognized under an input method – is a critical audit matter are there was significant judgment and estimation by management in determining the total estimated effort required to complete the performance obligation, specifically the estimation of forecasted direct labor and material costs, and external contract research organization costs. This in turn led to a high degree of auditor judgment, effort and subjectivity in performing procedures and in evaluating audit evidence relating to the cost estimates made by management.

Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming our overall opinion on the consolidated financial statements. These procedures included testing the effectiveness of controls relating to the revenue recognition process, including controls over the revenue recognized for research and development services, controls over the costs incurred to date for each performance obligation, and controls over the inputs and assumptions used to estimate the total effort required to complete each performance obligation. These procedures also included, among others, testing the actual costs incurred to date for each identified performance obligation, and evaluating and testing management's process for estimating total costs to complete each performance obligation which included evaluating the reasonableness of management's estimates of total forecasted direct labor and materials costs and total external contract research organization costs. Evaluating the reasonableness of the assumptions used involved evaluating the appropriateness of changes to management's estimates of total costs to complete and performing a comparison of management's prior period cost estimates to actual costs incurred.

/s/ PricewaterhouseCoopers LLP

Boston, Massachusetts
February 19, 2020

We have served as the Company's auditor since 2017.

Agios Pharmaceuticals, Inc.

Consolidated Balance Sheets

(In thousands) December 31:	2019	2018
Assets		
Current assets:		
Cash and cash equivalents	$ 80,931	$ 70,502
Marketable securities	483,946	514,800
Accounts receivable, net	8,952	5,076
Collaboration receivable – related party	1,539	2,462
Collaboration receivable – other	1,928	670
Royalty receivable – related party	2,900	2,234
Inventory	7,331	869
Prepaid expenses and other current assets	24,177	17,167
Total current assets	611,704	613,780
Marketable securities	152,929	220,119
Operating lease assets	93,643	—
Property and equipment, net	31,472	24,320
Financing lease assets	993	—
Other non-current assets	—	238
Total assets	$ 890,741	$ 858,457
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 21,896	$ 17,880
Accrued expenses	53,142	42,147
Deferred revenue – related party	10,933	32,710
Operating lease liabilities	6,642	—
Deferred rent	—	766
Financing lease liabilities	273	—
Total current liabilities	92,886	93,503
Deferred revenue, net of current portion – related party	50,580	59,809
Operating lease liabilities, net of current portion	106,074	—
Deferred rent, net of current portion	—	17,608
Financing lease liabilities, net of current portion	673	—
Total liabilities	250,213	170,920
Commitments and contingent liabilities (Note 9)		
Stockholders' equity:		
Preferred stock, $0.001 par value; 25,000,000 shares authorized, no shares issued and outstanding at December 31, 2019 and 2018	—	—
Common stock, $0.001 par value; 125,000,000 shares authorized and 68,401,105 and 58,218,653 shares issued and outstanding at December 31, 2019 and 2018, respectively	68	58
Additional paid-in capital	2,156,363	1,794,283
Accumulated other comprehensive income (loss)	202	(2,171)
Accumulated deficit	(1,516,105)	(1,104,633)
Total stockholders' equity	640,528	687,537
Total liabilities and stockholders' equity	$ 890,741	$ 858,457

See accompanying Notes to Consolidated Financial Statements.

Agios Pharmaceuticals, Inc.

Consolidated Statements of Operations

(In thousands, except share and per share data) Years Ended December 31:	2019	2018	2017
Revenues:			
Product revenue, net	$ 59,851	$ 13,841	$ —
Collaboration revenue – related party	39,257	60,661	41,074
Collaboration revenue – other	8,262	12,670	—
Royalty revenue – related party	10,542	7,215	1,937
Total revenue	117,912	94,387	43,011
Cost and expenses:			
Cost of sales	1,317	1,397	—
Research and development [(1)]	410,894	341,324	292,681
Selling, general and administrative	132,034	114,145	71,124
Total cost and expenses	544,245	456,866	363,805
Loss from operations	(426,333)	(362,479)	(320,794)
Interest income, net	14,861	16,451	6,124
Net loss	$ (411,472)	$ (346,028)	$ (314,670)
Net loss per share – basic and diluted	$ (6.86)	$ (6.03)	$ (6.75)
Weighted-average number of common shares used in computing net loss per share – basic and diluted	59,994,539	57,418,300	46,587,631

(1) Total research and development expenses are net of cost reimbursements from related party of $0, $0, and $7,811 for the years ended December 31, 2019, 2018 and 2017, respectively.

See accompanying Notes to Consolidated Financial Statements.

Agios Pharmaceuticals, Inc.

Consolidated Statements of Comprehensive Loss

(In thousands) Years Ended December 31:	2019	2018	2017
Net loss	$ (411,472)	$ (346,028)	$ (314,670)
Other comprehensive income (loss):			
Unrealized gain (loss) on available-for-sale securities	2,373	(782)	(1,076)
Comprehensive loss	$ (409,099)	$ (346,810)	$ (315,746)

See accompanying Notes to Consolidated Financial Statements.

Agios Pharmaceuticals, Inc.

Consolidated Statements of Stockholders' Equity

(In thousands, except share amounts)	Common Stock Shares	Common Stock Amount	Additional Paid-In Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Stockholders' Equity
Balance at December 31, 2016	42,220,444	$ 42	$ 842,013	$ (313)	$ (483,151)	$ 358,591
Unrealized loss on available-for-sale securities	—	—	—	(1,076)	—	(1,076)
Net loss	—	—	—	—	(314,670)	(314,670)
Stock-based compensation expense	—	—	47,809	—	—	47,809
Issuance of common stock under stock incentive and employee stock purchase plans	797,629	1	14,189	—	—	14,190
Issuance of common stock for follow-on offering	5,808,080	6	270,244	—	—	270,250
Other	—	—	649	—	(240)	409
Balance at December 31, 2017	48,826,153	$ 49	$ 1,174,904	$ (1,389)	$ (798,061)	$ 375,503
Unrealized loss on available-for-sale securities	—	—	—	(782)	—	(782)
Net loss	—	—	—	—	(346,028)	(346,028)
Adjustment to beginning accumulated deficit resulting from adoption of ASC 606	—	—	—	—	39,456	39,456
Stock-based compensation expense	—	—	73,357	—	—	73,357
Issuance of common stock under stock incentive and employee stock purchase plans	1,239,514	1	30,215	—	—	30,216
Issuance of common stock for follow-on offering	8,152,986	8	516,198	—	—	516,206
Other	—	—	(391)	—	—	(391)
Balance at December 31, 2018	58,218,653	$ 58	$ 1,794,283	$ (2,171)	$ (1,104,633)	$ 687,537
Unrealized gain on available-for-sale securities	—	—	—	2,373	—	2,373
Net loss	—	—	—	—	(411,472)	(411,472)
Stock-based compensation expense	—	—	72,373	—	—	72,373
Issuance of common stock under stock incentive and employee stock purchase plans	694,952	1	12,515	—	—	12,516
Issuance of common stock for follow-on offering	9,487,500	9	277,192	—	—	277,201
Other	—	—	—	—	—	—
Balance at December 31, 2019	68,401,105	$ 68	$ 2,156,363	$ 202	$ (1,516,105)	$ 640,528

See accompanying Notes to Consolidated Financial Statements.

Agios Pharmaceuticals, Inc.

Consolidated Statements of Cash Flows

(In thousands) Years Ended December 31:	2019	2018	2017
Operating activities			
Net loss	$ (411,472)	$ (346,028)	$ (314,670)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	8,087	7,172	6,432
Stock-based compensation expense	72,373	73,357	47,809
Net accretion of discount on marketable securities	(3,195)	(3,837)	(11)
Loss on disposal of property and equipment	1,052	20	40
Non-cash operating lease expense	8,532	—	—
Changes in operating assets and liabilities:			
Accounts receivable, net	(3,876)	(5,076)	—
Collaboration receivable – related party	923	(14)	2,438
Collaboration receivable – other	(1,258)	(670)	—
Royalty receivable – related party	(666)	(1,012)	(1,222)
Inventory	(6,462)	(869)	—
Prepaid expenses and other current and non-current assets	(7,742)	1,148	(3,600)
Accounts payable	3,716	(5,488)	5,329
Accrued expenses	7,233	8,623	1,522
Deferred revenue – related party	(31,006)	(31,665)	(26,570)
Operating lease liabilities	(6,861)	—	—
Deferred rent	—	(82)	(2,729)
Net cash used in operating activities	(370,622)	(304,421)	(285,232)
Investing activities			
Purchases of marketable securities	(488,566)	(933,320)	(688,702)
Proceeds from maturities and sales of marketable securities	592,177	666,481	635,421
Purchases of property and equipment	(12,171)	(6,986)	(4,627)
Net cash provided by (used in) investing activities	91,440	(273,825)	(57,908)
Financing activities			
Payments on financing lease obligations	(113)	—	—
Proceeds from public offering of common stock, net of reimbursements	277,201	516,206	270,250
Reimbursement (payment) of public offering costs	—	(391)	638
Net proceeds from stock option exercises and employee stock purchase plan	12,523	30,209	14,222
Net cash provided by financing activities	289,611	546,024	285,110
Net change in cash and cash equivalents	10,429	(32,222)	(58,030)
Cash and cash equivalents at beginning of the period	70,502	102,724	160,754
Cash and cash equivalents at end of the period	$ 80,931	$ 70,502	$ 102,724
Supplemental disclosure of non-cash investing and financing transactions:			
Additions to property and equipment in accounts payable and accrued expenses	$ 5,168	$ 1,106	$ 1,011
Proceeds from stock option exercises in other current assets	$ —	$ 7	$ —
Operating lease liabilities arising from obtaining operating lease assets	$ 42,322	$ —	$ —
Financing lease liabilities arising from obtaining financing lease assets	$ 1,052	$ —	$ —

See accompanying Notes to Consolidated Financial Statements.

Note 1. Nature of Business

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.

Overview

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 creating differentiated, small molecule medicines for patients in the areas of hematologic malignancies, solid tumors and rare genetic diseases, or RGDs. To address these focus areas, 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. We are located in Cambridge, Massachusetts.

Our wholly-owned product, TIBSOVO® (ivosidenib) is an oral targeted inhibitor of the mutated isocitrate dehydrogenase 1, or IDH1 enzyme. TIBSOVO® is the first and only U.S. Food and Drug Administration, or FDA-approved therapy for the treatment of adult patients with (i) relapsed or refractory acute myeloid leukemia, or R/R AML, with a susceptible IDH1 mutation as detected by an FDA-approved test (approved by the FDA in July 2018) and (ii) newly diagnosed AML with a susceptible IDH1 mutation as detected by an FDA-approved test who are at least 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy (approved by the FDA in May 2019). In December 2018, we submitted an Marketing Authorization Application, or MAA, to the European Medicines Agency, or EMA, for TIBSOVO® for the treatment of adult patients with R/R AML with an IDH1 mutation.

Our other marketed product is IDHIFA® (enasidenib), an oral targeted inhibitor of the mutated isocitrate dehydrogenase 2, or IDH2 enzyme and the first and only FDA-approved therapy for patients with R/R AML and an IDH2 mutation. 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. 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. In June 2018, Celgene submitted an MAA to the EMA for IDHIFA® for IDH2 mutant-positive AML which it subsequently withdrew in December 2019.

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

Vorasidenib is an orally available, selective brain-penetrant pan-IDH mutant inhibitor. We are developing vorasidenib for the treatment of IDH mutant-positive low grade glioma and are currently evaluating vorasidenib in clinical trials.

AG-270 is an orally available selective potent inhibitor of methionine adenosyltransferase 2a, or MAT2A. We are currently evaluating AG-270 in a phase 1 dose-escalation and expansion trial in multiple tumor types carrying a methylthioadenosine phosphorylase, or MTAP, deletion.

AG-636 is an inhibitor of the metabolic enzyme dihydroorotate dehydrogenase, or DHODH. We are currently evaluating AG-636 in the phase 1 dose-escalation trial in lymphoma.

The lead product candidate in our RGD portfolio, mitapivat, is an activator of both wild-type and mutant pyruvate kinase-R for the potential treatment of hemolytic anemias. We are currently evaluating mitapivat for the treatment of pyruvate kinase, or PK, deficiency, thalassemia and sickle cell disease, or SCD, in clinical trials.

In addition to the aforementioned development programs, we are seeking to advance a number of early-stage discovery programs in our focus areas of malignant hematology, solid tumors and RGDs based on our scientific leadership in the field of cellular metabolism and adjacent areas of biology.

We are subject to risks common to companies in our industry including, but not limited to, uncertainties relating to conducting clinical research and development, the manufacture and supply of products for clinical and commercial use, obtaining and maintaining regulatory approvals and pricing and reimbursement for our products, market acceptance, managing global growth and operating expenses, availability of additional capital, competition, obtaining and enforcing patents, stock price volatility, dependence on collaborative relationships and third-party service providers, dependence on key personnel, potential litigation, product liability claims and government investigations.

Liquidity

In November 2019, we completed a public offering of 8,250,000 shares of common at an offering price of $31.00 per share. We received net proceeds from this offering of $241.0 million, after deducting underwriting discounts and commissions paid by us. In addition, we granted the underwriters the right to purchase up to an additional 1,237,500 shares of common stock, which was exercised in November 2019, resulting in additional net proceeds to us of $36.2 million, after underwriting discounts and commissions. After giving effect to the full exercise of the over-allotment option, the number of shares sold by us in the public offering totaled 9,487,500 shares, and net proceeds to us totaled $277.2 million, after underwriting discounts and commissions.

As of December 31, 2019, we had cash, cash equivalents and marketable securities of $717.8 million. Although we have incurred recurring losses and expect to continue to incur losses for the foreseeable future, we expect our cash, cash equivalents and marketable securities to be sufficient to fund current operations for at least the next twelve months from the issuance of the financial statements. If the Company is unable to raise additional funds through equity or debt financings, the Company may be required to delay, limit, reduce or terminate product development or future commercialization efforts or grant rights to develop and market products or product candidates that the Company would otherwise prefer to develop and market itself.

Note 2. Summary of Significant Accounting Policies

Principles of consolidation

The consolidated financial statements include our accounts and the accounts of our wholly owned subsidiaries, Agios Securities Corporation, Agios International Sarl, Agios Germany GmbH, Agios Netherlands B.V., and Agios Limited. All intercompany transactions have been eliminated in consolidation. The consolidated financial statements have been prepared in conformity with U.S. generally accepted accounting principles, or U.S. GAAP.

Use of estimates

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

Cash and cash equivalents

We consider highly liquid investments with a maturity of three months or less when purchased to be cash equivalents. Cash equivalents are stated at fair value.

Marketable securities

Marketable securities at December 31, 2019 and 2018 consisted of investments in certificates of deposit, U.S. Treasuries, government securities and corporate debt securities. We determine the appropriate classification of the securities at the time they are acquired and evaluate the appropriateness of such classifications at each balance sheet date. We classify our marketable securities as available-for-sale pursuant to Accounting Standards Codification, or ASC, 320, *Investments – Debt and Equity Securities*. Marketable securities are recorded at fair value, with unrealized gains and losses included as a component of accumulated other comprehensive loss in stockholders' equity and a component of total comprehensive loss in the consolidated statements of comprehensive loss, until realized. Realized gains and losses are included in investment income on a specific-identification basis.

At December 31, 2019 and 2018, we held both current and non-current investments. Investments classified as current have maturities of less than one year. Investments classified as non-current are those that: (i) have a maturity of one to two years, and (ii) we do not intend to liquidate within the next twelve months, although these funds are available for use and therefore classified as available-for-sale.

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

Fair value measurements

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

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

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

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

Our financial assets, which include cash equivalents and marketable securities, have been initially valued at the transaction price, and subsequently revalued at the end of each reporting period, utilizing third-party pricing services or other observable market data. The pricing services utilize industry standard valuation models, including both income and market based approaches, and observable market inputs to determine value. After completing our validation procedures, we did not adjust or override any fair value measurements provided by the pricing services as of December 31, 2019 or 2018. Fair value information for these assets, including their classification in the fair value hierarchy is included in Note 3. *Fair Value Measurements***.**

There have been no changes to the valuation methods during the years ended December 31, 2019 and 2018. We evaluate transfers between levels at the end of each reporting period.

The carrying amounts of collaboration receivable – related party, collaboration receivable – other, royalty receivable – related party, accounts receivable, prepaid expenses and other current assets, accounts payable, and accrued expenses approximate their fair values due to their short-term maturities.

Accounts receivable, net

Our trade accounts receivable arise from product sales and represent amounts due from specialty distributors and specialty pharmacy providers in the U.S. We monitor the financial performance and creditworthiness of our customers so that we can properly assess and respond to changes in their credit profile. We reserve against these receivables for estimated losses that may arise from a customer's inability to pay. Amounts determined to be uncollectible are charged or written-off against the reserve.

Concentrations of credit risk

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

We are also subject to credit risk on our receivables, including trade receivables from our customers and collaboration and royalty receivables from Celgene and CStone Pharmaceuticals, or CStone. Concentrations of credit risk with respect to receivables, which are typically unsecured, are somewhat mitigated due to the number of customers using our products. Our trade receivables arise from product sales in the U.S. and have standard payment terms that generally require payment within 30 to 60 days. We have evaluated the creditworthiness of our customers, including Celgene, and determined them to be creditworthy. To date we have not experienced any losses with respect to our receivables.

Inventory

Inventory is stated at the lower of cost or estimated net realizable value on a first-in, first-out basis. Prior to the regulatory approval of our product candidates, we incur expenses for the manufacture of drug product that could potentially be available to support the commercial launch of those products. Until the date at which regulatory approval has been received or is otherwise considered probable, we record all such costs as research and development expenses. Upon approval of our wholly owned product, TIBSOVO®, by the FDA on July 20, 2018 for the treatment of adult patients with R/R AML with susceptible IDH1 mutation as detected by an FDA-approved test, we began to capitalize inventories of TIBSOVO®.

We perform an assessment of the recoverability of capitalized inventory during each reporting period and write down any excess and obsolete inventory to its estimated net realizable value in the period in which the impairment is first identified. Such impairment charges, should they occur, are recorded as a component of cost of sales in the consolidated statements of operations. The determination of whether inventory costs will be realizable requires the use of estimates by management. If

actual market conditions are less favorable than projected by management, additional write-downs of inventory may be required.

Property and equipment

Property and equipment consist of laboratory equipment, computer equipment and software, leasehold improvements, furniture and fixtures, and office equipment. Costs of major additions and betterment are capitalized; maintenance and repairs, which do not improve or extend the life of the respective assets, are charged to expense as incurred. Upon retirement or sale, the cost of the disposed asset and the related accumulated depreciation are removed from the accounts and the resulting gain or loss is recognized.

Property and equipment is stated at cost, and depreciated using the straight-line method over the estimated useful lives of the respective assets:

	Years
Laboratory equipment	5
Computer equipment and software	3
Furniture and fixtures	5
Office equipment	5

Leasehold improvements are amortized over the lesser of the remaining lease term or the estimated useful life of the improvement.

Impairment of long-lived assets

We periodically evaluate our long-lived assets for potential impairment in accordance with ASC 360, *Property, Plant and Equipment*. Potential impairment is assessed when there is evidence that events or changes in circumstances indicate that the carrying amount of an asset may not be recovered. Recoverability of these assets is assessed based on the undiscounted expected future cash flows from the assets, considering a number of factors, including past operating results, budgets and economic projections, market trends and product development cycles. If impairments are identified, assets are written down to their estimated fair value. We did not recognize any impairment charges through December 31, 2019.

Leases

We determine if an arrangement is a lease at inception. An arrangement is determined to contain a lease if the contract conveys the right to control the use of an identified property or equipment for a period of time in exchange for consideration. If we can benefit from the various underlying assets of a lease on their own or together with other resources that are readily available, or if the various underlying assets are neither highly dependent on nor highly interrelated with other underlying assets in the arrangement, they are considered to be a separate lease component. In the event multiple underlying assets are identified, the lease consideration is allocated to the various components based on each of the component's relative fair value.

Operating lease assets represent our right to use an underlying asset for the lease term and operating lease liabilities represent our obligation to make lease payments arising from the leasing arrangement. Operating lease assets and operating lease liabilities are recognized at commencement date based on the present value of lease payments over the lease term. As most of our leases do not provide an implicit rate, in determining the operating lease liabilities, we use an estimate of our incremental borrowing rate. The incremental borrowing rate is determined using two alternative credit scoring models to estimate our credit rating, adjusted for collateralization. The calculation of the operating lease assets includes any lease payments made and excludes any lease incentives. Our lease terms may include options to extend or terminate the lease when it is reasonably certain that we will exercise that option.

For operating leases, we record operating lease assets and lease liabilities in our consolidated balance sheets. Lease expense for lease payments is recognized on a straight-line basis over the lease term. Short-term leases, or leases that have a lease term of 12 months or less at commencement date, are excluded from this treatment and are recognized on a straight-line basis over the term of the lease.

We have not entered into any material short-term leases or financing leases as of December 31, 2019.

Revenue from contracts with customers

On January 1, 2018 we adopted ASC 606, *Revenue from Contracts with Customers*, under the modified retrospective method. Prior to January 1, 2018 we accounted for the consideration received under the Collaboration Agreements under ASC 605-25, *Multiple Element Arrangements.*

In adopting ASC 606, we applied the practical expedient that permits aggregating the effect of all contract modifications that occurred prior to January 1, 2018. No other practical expedients were used. Similar to the accounting under ASC 605-25, the 2016 Agreement was determined to be a modification of the 2010 Agreement and the AG-881 Agreements with Celgene.

Revenue is recognized when the customer obtains control of promised goods or services, in an amount that reflects the consideration that we expect to receive in exchange for those goods or services. To determine revenue recognition for arrangements that we determined to be within the scope of ASC 606, we perform the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) we satisfy a performance obligation. We only apply the five-step model to contracts when it is probable that we will collect the consideration we are entitled to in exchange for the goods or services we transfer to the customer. At contract inception, once the contract is determined to be within the scope of ASC 606, we assess the goods or services promised within each contract and determine those that are performance obligations, and assess whether each promised good or service is distinct. We will then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

Product revenue

We generate product revenue from sales of TIBSOVO® to a limited number of specialty distributors and specialty pharmacy providers in the U.S., or collectively, the Customers. The Customers subsequently resell TIBSOVO® to pharmacies or dispense directly to patients. In addition to distribution agreements with Customers, we enter into arrangements with healthcare providers and payors that provide for government-mandated and/or privately-negotiated rebates, chargebacks and discounts with respect to the purchase of TIBSOVO®.

The performance obligation related to the sale of TIBSOVO® is satisfied and revenue is recognized when the Customer obtains control of the product, which occurs at a point in time, typically upon delivery to the Customer.

Revenues from product sales are recorded at the net sales price, or transaction price, which includes estimates of variable consideration for which reserves are established and result from contractual adjustments, government rebates, returns and other allowances that are offered within the contracts with our Customers, healthcare providers, payors and other indirect customers relating to the sale of our products.

Contractual adjustments. We generally provide Customers with discounts, including prompt pay discounts, and allowances that are explicitly stated in the contracts and are recorded as a reduction of revenue in the period the related product revenue is recognized.

Chargebacks and discounts represent the estimated obligations resulting from contractual commitments to sell products to qualified healthcare providers at prices lower than the list prices charged to Customers who directly purchase the product from us. Customers charge us for the difference between what they pay for the product and the ultimate selling price to the qualified healthcare providers. These reserves are estimated using the expected value method, based upon a range of possible outcomes that are probability-weighted for the estimated channel mix and are established in the same period that the related revenue is recognized, resulting in a reduction of product revenue.

Government rebates. Government rebates consist of Medicare, TriCare, and Medicaid rebates, which we estimate using the expected value method, based upon a range of possible outcomes that are probability-weighted for the estimated payor mix. These reserves are recorded in the same period the related revenue is recognized, resulting in a reduction of product revenue. For Medicare, we also estimate the number of patients in the prescription drug coverage gap for whom we will owe an additional liability under the Medicare Part D program.

Returns. We estimate the amount of product sales that may be returned by Customers and record this estimate as a reduction of revenue in the period the related product revenue is recognized. We currently estimate product return liabilities using the expected value method, based on available industry data, including our visibility into the inventory remaining in the distribution channel.

Collaboration revenue

We apply the provisions of ASC 808, *Collaborative Arrangements,* when accounting for our collaboration agreements. We evaluate the presentation of amounts due from our collaborative partners associated with activities in the collaborative arrangement based on the nature of each activity. For transactions with customers, we have reported revenues and costs in accordance with ASC 606, *Revenue from Contracts with Customers*, ASC 606-10-55-36 through 55-40, *Principal versus Agent Considerations*. We recognize revenue when the customer obtains control of promised goods or services, in an amount that reflects the consideration that we expect to receive in exchange for those goods or services. To determine revenue recognition for arrangements that have been determined to be within the scope of ASC 606, we perform the following five steps: (i) identify

the contract(s) with a customer; (ii) identify the performance obligations in the contract based on the relative standalone selling prices of the goods or services provided; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) we satisfy a performance obligation. We only apply the five-step model to contracts when it is probable that we will collect the consideration we are entitled to in exchange for the goods or services we transfer to the customer.

Once the contract is determined to be within the scope of ASC 606, we assess the goods or services promised within each contract and determine those that are performance obligations, and assess whether each promised good or service is distinct. We will then recognize as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

The transaction price for each collaboration agreement is determined based on the amount of consideration we expect to be entitled to for satisfying all performance obligations within the agreement. Significant judgment may be required in determining the amount of variable consideration to be included in the transaction price. We use the expected value methods to determine variable consideration and will re-evaluate the transaction price in each reporting period and as uncertain events are resolved or other changes in circumstances occur.

As part of the initial accounting for these arrangements, we must develop assumptions that require judgment to determine the standalone selling price, or SSP, for each performance obligation identified in the contract. We use these key assumptions to determine the SSP, which include forecast of revenues, development timelines, reimbursement rates for personnel costs, discount rates and probabilities of technical and regulatory success.

We recognize the transaction price allocated to upfront license payments as revenue upon delivery of the license to the customer and resulting ability of the customer to use and benefit from the license, if the license is determined to be distinct from the other performance obligations identified in the contract. If the license is considered to not be distinct from other performance obligations, we exercise judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied (i) at a point in time, but only for licenses determined to be distinct from other performance obligations in the contract, or (ii) over time; and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from license payments. We evaluate the measure of progress each reporting period and, if necessary, adjust the measure of performance and related revenue recognition.

A significant portion of revenue generated from our collaboration agreements with Celgene relates to the provision of research and development services whereby revenue is recognized under an input method using the ratio of effort incurred to date compared to the total estimated effort required to complete the performance obligation. The calculation of the total estimated effort includes the total amount of forecasted costs associated with the completion of discovery, pre-clinical or clinical trials, as well as the assumed timing of these activities and estimated patient populations. Such cost estimates include forecasted direct labor and material costs, subcontractor costs, and external contract research organization, or CRO, costs.

Milestone revenue

Many of our collaboration agreements also entitle us to additional payments upon the achievement of performance-based milestones. These milestones are generally categorized into three types: development milestones, which are generally based on the initiation of clinical trials; regulatory milestones, which are generally based on the submission, filing or approval of regulatory applications such as a new drug application, or NDA, in the U.S.; and sales-based milestones, which are generally based on meeting specific thresholds of sales in certain geographic areas during a specified period. Upfront and ongoing development milestones per our collaboration agreements are not subject to refund if the development activities are not successful.

For each collaboration that includes development milestone payments, we evaluate whether it is probable that the consideration associated with each milestone will not be subject to a significant reversal in the cumulative amount of revenue recognized. Amounts that meet this threshold are included in the transaction price using the most likely amount method, whereas amounts that do not meet this threshold are considered constrained and excluded from the transaction price until they meet this threshold. Milestones tied to regulatory approval, and therefore not within our control, are considered constrained until such approval is received. At the end of each subsequent reporting period, we re-evaluate the probability of a significant reversal of the cumulative revenue recognized for our milestones, and, if necessary, adjust our estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues from collaborators and loss in the period of adjustment. For arrangements that include sales-based milestone or royalty payments based on the level of sales, and in which the license is deemed to be the predominant item to which the sales-based milestone or royalties relate to, we recognize revenue in the period in which the sales-based milestone is achieved and in the period in which the sales associated with the royalty occur.

Adoption of ASC 606

We adopted ASC 606 using the modified retrospective method. Under this method, we recognized the cumulative effect of the change in the opening balance of accumulated deficit in the December 31, 2018 consolidated balance sheet.

In adopting ASC 606, we applied the practical expedient that permits aggregating the effect of all contract modifications that occurred prior to January 1, 2018. No other practical expedients were used.

The impact of the cumulative effect of the accounting changes upon the adoption of the standard is as follows:

(In thousands)	December 31, 2017	Cumulative Effect	January 1, 2018
Deferred revenue – related party, current and net of current portions	$ 163,640	$ (39,456)	$ 124,184
Accumulated deficit	(798,061)	39,456	(758,605)

The following tables summarize the effects of adopting ASC 606 on our consolidated financial statements:

Consolidated Balance Sheets	December 31, 2018		
(In thousands)	Under Topic 606	Under Topic 605	Effect of Change
Accounts receivable, net	$ 5,076	$ 5,076	$ —
Collaboration receivable – related party	2,462	2,462	—
Collaboration receivable – other	670	230	440
Total current assets	613,780	613,340	440
Total assets	858,457	858,017	440
Deferred revenue – related party	32,710	29,133	3,577
Total current liabilities	93,503	89,926	3,577
Deferred revenue, net of current portion – related party	59,809	101,180	(41,371)
Total liabilities	170,920	208,714	(37,794)
Accumulated deficit	(1,104,633)	(1,142,867)	38,234
Total stockholders' equity	687,537	649,303	38,234
Total liabilities and stockholders' equity	858,457	858,017	440

Consolidated Statements of Operations	Year ended December 31, 2018		
(In thousands, except per share data)	Under Topic 606	Under Topic 605	Effect of Change
Product revenue, net	$ 13,841	$ 13,841	$ —
Collaboration revenue – related party	60,661	58,994	1,667
Collaboration revenue – other	12,670	12,230	440
Total revenue	94,387	92,280	2,107
Research and development expense	341,324	337,995	3,329
Total cost and expenses	456,866	453,537	3,329
Loss from operations	(362,479)	(361,257)	(1,222)
Net loss	(346,028)	(344,806)	(1,222)
Net loss per share – basic and diluted	(6.03)	(6.01)	(0.02)

Consolidated Statements of Comprehensive Loss	Year ended December 31, 2018		
(In thousands)	Under Topic 606	Under Topic 605	Effect of Change
Net loss	$ (346,028)	$ (344,806)	$ (1,222)
Comprehensive loss	(346,810)	(345,588)	(1,222)

Consolidated Statements of Cash Flows	Year ended December 31, 2018		
(In thousands)	Under Topic 606	Under Topic 605	Effect of Change
Net loss	$ (346,028)	$ (344,806)	$ (1,222)
Adjustments to reconcile net loss to net cash used in operating activities:			
Accounts receivable, net	(5,076)	(5,076)	—
Collaboration receivable – related party	(14)	(14)	—
Collaboration receivable – other	(670)	(230)	(440)
Deferred revenue – related party	(31,665)	(33,327)	1,662

Cost of Sales

Cost of sales consists primarily of manufacturing costs of TIBSOVO®. Based on our policy to expense costs associated with the manufacturing of our products prior to regulatory approval, certain of the manufacturing costs associated with product shipments of TIBSOVO® recorded during the years ended December 31, 2019 and December 31, 2018 were expensed prior to July 20, 2018 and, therefore, are not included in costs of sales during the years ended December 31, 2019 or 2018.

Research and development costs

Research and development costs, including those accrued as of each balance sheet date, are expensed as incurred. These costs include salaries and personnel-related costs, consulting fees, fees paid for contract research services, fees paid to contract CROs, and other third parties in connection with clinical trials and preclinical development activities, fees paid to investigative sites in connection with clinical studies, the costs associated with the product manufacturing, development, and distribution of clinical supplies, the costs of laboratory equipment and facilities, and other external costs.

Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are deferred and capitalized. Additionally, there may be instances in which payments made to our vendors will exceed the level of services provided, and result in a prepayment of the research and development expense. The capitalized amounts are expensed as the related goods are delivered or the services are performed. We estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid accordingly.

Stock-based compensation

We account for stock-based compensation awards in accordance with ASC 718, *Compensation –Stock Compensation*, or ASC 718. For stock-based awards granted to employees and to members of the board of directors for their services and for participation in our employee stock purchase plan, we primarily estimate the grant date fair value of each option award using the Black-Scholes option-pricing model. The use of the Black-Scholes option-pricing model requires us to make assumptions with respect to the expected term of the option, the expected volatility of the common stock consistent with the expected life of the option, risk-free interest rates and expected dividend yields of the common stock. For awards subject to service-based vesting conditions, we recognize stock-based compensation expense equal to the grant date fair value of stock options on a straight-line basis over the requisite service period. For awards subject to both performance and service-based vesting conditions, we recognize stock-based compensation expense over the remaining service period if the performance condition is considered probable of achievement using management's best estimates.

In 2017, we adopted ASU 2016-09, *Compensation—Stock Compensation (Topic 718): Improvements to Employee Share-Based Payment Accounting*, which simplifies several aspects of the accounting for employee share-based payment transactions, including income tax consequences, classification of awards as either equity or liabilities, and classification in the statement of

cash flows. Upon adoption of this standard, we recorded a cumulative-effect adjustment of approximately $32.7 million through retained earnings and deferred tax assets.

Income taxes

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

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

Comprehensive income (loss)

Comprehensive income (loss) is defined as the change in equity of a business enterprise during a period from transactions, and other events and circumstances, and currently consists of net loss and unrealized gains and losses on available-for-sale securities. Accumulated other comprehensive loss consists entirely of unrealized gains and losses from available-for-sale securities as of December 31, 2019 and 2018.

Net loss per share

Basic net loss per share is calculated by dividing net loss by the weighted-average shares outstanding during the period, without consideration for common stock equivalents. Diluted net loss per share is calculated by adjusting weighted-average shares outstanding for the dilutive effect of common stock equivalents outstanding for the period, determined using the treasury-stock method. For purposes of the dilutive net loss per share calculation, stock options, restricted stock units, performance-based stock units and market-based stock units for which the performance vesting conditions have been met, and employee stock purchase plan shares are considered to be common stock equivalents but are excluded from the calculation of diluted net loss per share as their effect would be anti-dilutive.

Segment and geographic information

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

Recent accounting pronouncements

Leases

In February 2016, the FASB issued ASU 2016-02, *Leases (Topic 842)*, which was codified as ASC 842, *Leases*, and amended through subsequent ASUs. We adopted ASC 842 effective January 1, 2019 using the optional transition method provided for under ASU 2018-11, *Leases (Topic 842): Targeted Improvements*, whereby we applied the new lease requirements through a cumulative-effect adjustment, which after completing our implementation analysis, resulted in no material adjustment to our January 1, 2019 beginning accumulated deficit balance. We also elected the package of practical expedients provided for under ASU 2018-11, which allows us not to reassess whether contracts are or contain leases, lease classification, and whether initial direct costs qualify for capitalization. Additionally, as an accounting policy, for our building leases, we chose not to separate the non-lease components from the lease components and, instead, accounted for each non-lease component and lease component as a single component.

We completed our assessment over the impact of the standard and determined that the only material leases that we hold are our building leases. Upon adoption of the standard on January 1, 2019, we recorded operating right of use assets of $59.9 million and operating lease liabilities of $77.3 million on our consolidated balance sheets. Prior periods are presented in accordance with ASC 840, *Leases*.

Other recent accounting pronouncements

In June 2018, the FASB issued Accounting Standards Update No. 2018-07 – *Compensation-Stock Compensation (Topic 718)-Improvements to Nonemployee Share-Based Payment Accounting*. ASU 2018-07 simplifies the accounting for share-based

payments to nonemployees by aligning it with the accounting for share-based payments to employees, with certain exceptions. ASU 2018-07 is effective for fiscal years beginning after December 15, 2018. The Company adopted the new standard as of January 1, 2019. There was no material impact to the Company's consolidated financial position, results of operation, or cash flows.

In December 2019, the FASB issued Accounting Standards Update No. 2019-12 – *Income Taxes (Topic 740) Simplifying the Accounting for Income Taxes,* as part of its initiative to reduce complexity in the accounting standards. The amendments in ASU 2019-12 eliminate certain exceptions related to the approach for intraperiod tax allocation, the methodology for calculating income taxes in an interim period and the recognition of deferred tax liabilities for outside basis differences. ASU 2019-12 also clarifies and simplifies other aspects of the accounting for income taxes. The amendments in ASU 2019-12 are effective for the fiscal years beginning after December 15, 2020. Early adoption is permitted, including adoption in any interim period. The Company has early adopted this amendment as of January 1, 2019. There was no material impact to the Company's consolidated financial position, results of operation, or cash flows.

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

Subsequent events

We considered events or transactions occurring after the balance sheet date, but prior to the issuance of the consolidated financial statements, for potential recognition or disclosure in our consolidated financial statements. All significant subsequent events have been properly disclosed in the consolidated financial statements.

Note 3. Fair Value Measurements

The following table summarizes our cash equivalents and marketable securities measured at fair value and by level (as described in Note 2. *Summary of Significant Accounting Policies*) on a recurring basis as of December 31, 2019:

(In thousands)	Level 1	Level 2	Level 3	Total
Cash equivalents	$ 12,568	$ 36,299	$ —	$ 48,867
Total cash equivalents	12,568	36,299	—	48,867
Marketable securities:				
Certificates of deposit	—	—	—	—
U.S. Treasuries	—	214,027	—	214,027
Government securities	—	97,820	—	97,820
Corporate debt securities	—	325,028	—	325,028
Total marketable securities	—	636,875	—	636,875
Total cash equivalents and marketable securities	$ 12,568	$ 673,174	$ —	$ 685,742

There were no transfers between Level 1 and Level 2 and we had no financial assets or liabilities that were classified as Level 3 at any point during the year ended December 31, 2019.

Note 4. Marketable Securities

Marketable securities at December 31, 2019 consisted of the following:

(In thousands)	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
Current:				
Certificates of deposit	$ —	$ —	$ —	$ —
U.S. Treasuries	178,721	58	(38)	178,741
Government securities	80,228	17	(16)	80,229
Corporate debt securities	224,928	139	(91)	224,976
Total Current	483,877	214	(145)	483,946
Non-current:				
U.S. Treasuries	35,296	3	(13)	35,286
Government securities	17,587	14	(10)	17,591
Corporate debt securities	99,913	239	(100)	100,052
Total Non-current	152,796	256	(123)	152,929
Total marketable securities	$ 636,673	$ 470	$ (268)	$ 636,875

Marketable securities at December 31, 2018 consisted of the following:

(In thousands)	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
Current:				
Certificates of deposit	$ 960	$ —	$ (4)	$ 956
U.S. Treasuries	231,101	7	(228)	230,880
Government securities	75,335	—	(121)	75,214
Corporate debt securities	208,233	—	(483)	207,750
Total Current	515,629	7	(836)	514,800
Non-current:				
U.S. Treasuries	12,202	4	(125)	12,081
Government securities	70,177	10	(188)	69,999
Corporate debt securities	139,082	12	(1,055)	138,039
Total Non-current	221,461	26	(1,368)	220,119
Total marketable securities	$ 737,090	$ 33	$ (2,204)	$ 734,919

There were no material realized gains or losses on marketable securities for the years ended December 31, 2019 and 2018.

At December 31, 2019 and 2018, we held 113 and 242 debt securities that were in an unrealized loss position for less than one year, respectively. The aggregate fair value of debt securities in an unrealized loss position at December 31, 2019 and 2018 was $345.7 million and $639.3 million, respectively. There were no individual securities that were in a significant unrealized loss position as of December 31, 2019 and 2018. Given our intent and ability to hold such securities until recovery, and the lack of material change in the credit risk of these investments, we do not consider these marketable securities to be other-than-temporarily impaired as of December 31, 2019 and 2018.

Note 5. Property and Equipment, net

Property and equipment, net consisted of the following at December 31:

(In thousands)	2019	2018
Laboratory equipment	$ 23,418	$ 20,165
Computer equipment and software	6,415	5,449
Leasehold improvements	23,879	22,084
Furniture and fixtures	2,101	1,065
Office equipment	589	407
Construction in progress	7,182	1,302
Total property and equipment	63,584	50,472
Less: accumulated depreciation	(32,112)	(26,152)
Total property and equipment, net	$ 31,472	$ 24,320

Depreciation expense for the years ended December 31, 2019, 2018 and 2017 was $8.0 million, $7.2 million and $6.4 million, respectively.

Note 6. Inventory

Inventory consisted of the following at December 31:

(In thousands)	2019	2018
Raw materials	$ 180	$ —
Work-in-process	6,808	788
Finished goods	343	81
Total Inventory	$ 7,331	$ 869

Inventory is related to our approved product, TIBSOVO®. There were no write downs for excess and obsolete inventory during the years ended December 31, 2019, 2018 or 2017.

Note 7. Leases

Our building leases are comprised of office and laboratory space under non-cancelable operating leases. These lease agreements have remaining lease terms of eight years and contain various clauses for renewal at our option. The renewal options were not included in the calculation of the operating lease assets and the operating lease liabilities as the renewal option is not reasonably certain of being exercised. The lease agreements do not contain residual value guarantees. Operating lease costs for the year ended December 31, 2019 were $15.1 million, and cash paid for amounts included in the measurement of operating lease liabilities for the year ended December 31, 2019 was $12.8 million.

On April 11, 2019, we entered into an agreement to lease approximately 13,000 square feet of office space located at 38 Sidney Street, Cambridge, Massachusetts, or the 38 Sidney Lease, with Thirty-Eight Sidney Street, LLC. The initial term of the 38 Sidney Lease commenced on May 1, 2019 and expires on February 29, 2028. At the end of the lease term, we have the option to extend the 38 Sidney Lease for two consecutive terms of five years at fair market rent at the time of the extension. The 38 Sidney Lease provides us with the right to lease additional space within the 38 Sidney Street building and also includes rent escalation clauses and a tenant improvement allowance of $1.0 million.

In connection with the 38 Sidney Lease, we also amended our existing building leases at 88 Sidney Street, Cambridge, Massachusetts and at 64 Sidney Street, Cambridge, Massachusetts to extend the initial terms of those leases by approximately three years through February 29, 2028. The amendments also provide us with the right to lease additional space at the 64 Sidney Street building. Our existing extension options for the 88 Sidney Street building and 64 Sidney Street building continue as set forth in the existing leases for those buildings.

We have not entered into any material short-term leases or financing leases as of December 31, 2019.

In arriving at the operating lease liabilities as of December 31, 2019, we applied the weighted-average incremental borrowing rate of 5.7% over a weighted-average remaining lease term of 8.2 years.

As of December 31, 2019, undiscounted minimum rental commitments under non-cancelable leases, for each of the next five years and total thereafter, were as follows:

(In thousands)		
2020	$	13,242
2021		14,380
2022		16,773
2023		18,126
2024		18,660
Thereafter		63,891
Undiscounted minimum rental commitments		145,072
Interest		(32,356)
Total operating lease liabilities	$	112,716

As of December 31, 2018, minimum rental commitments under non-cancelable leases, for each of the next five years and total thereafter, were as follows:

(In thousands)		
2019	$	12,759
2020		13,135
2021		13,473
2022		15,552
2023		17,145
Thereafter		19,223
Total minimum rental commitments	$	91,287

Rental expense under these leases, net of tenant improvement reimbursements, amounted to $11.4 million, and $6.0 million for the years ended December 31, 2018 and 2017, respectively. In addition to rent, the leases may require us to pay additional amounts for taxes, insurance, maintenance and other operating expenses.

We provided our landlord a standby letter of credit of $2.9 million as security for our leases. We are not required to maintain any cash collateral for the standby letter of credit.

Note 8. Accrued Expenses

Accrued expenses and other current liabilities consisted of the following at December 31:

(In thousands)		2019		2018
Accrued compensation	$	18,982	$	20,843
Accrued research and development costs		21,777		14,777
Accrued professional fees		8,335		5,441
Accrued other		4,048		1,086
Total accrued expenses	$	53,142	$	42,147

Note 9. Commitments and Contingent Liabilities

Manufacturing Commitments

We are party to various agreements with contract manufacturing organizations that we are not contractually able to terminate for convenience and avoid any and all future obligations to the vendors. Under such agreements, we are obligated to make certain minimum payments, with the exact amounts in the event of termination to be based on the timing of the termination and the exact terms of the agreement.

Legal Contingencies

From time to time, we may be involved in disputes and legal proceedings in the ordinary course of business. These proceedings may include allegations of infringement of intellectual property, employment or other matters. We do not have any ongoing legal proceedings that, based on our estimates, could have a material effect on our consolidated financial statements.

Note 10. Product Revenue

Our wholly owned product, TIBSOVO®, received approval from the FDA on July 20, 2018 for the treatment of adult patients with R/R AML with a susceptible IDH1 mutation. Upon FDA approval of TIBSOVO® in the U.S., we began generating product revenue from U.S. sales of TIBSOVO®.

(In thousands)	2019	2018	2017
Product revenue, net	$ 59,851	$ 13,841	$ —

The following table summarizes balances and activity in each of the product revenue allowance and reserve categories for the year ended December 31, 2019:

(In thousands)	Contractual Adjustments	Government Rebates	Returns	Total
Balance at December 31, 2018	592	325	334	1,251
Current provisions relating to sales in the current year	7,899	2,387	1,464	11,750
Adjustments relating to prior years	8	(41)	—	(33)
Payments/returns relating to sales in the current year	(7,027)	(1,286)	—	(8,313)
Payments/returns relating to sales in the prior years	(598)	(261)	—	(859)
Balance at December 31, 2019	874	1,124	1,798	3,796

The following table summarizes balances and activity in each of the product revenue allowance and reserve categories for the year ended December 31, 2018:

(In thousands)	Contractual Adjustments	Government Rebates	Returns	Total
Balance at December 31, 2017	—	—	—	—
Current provisions relating to sales in the current year	1,777	422	334	2,533
Adjustments relating to prior years	—	—	—	—
Payments/returns relating to sales in the current year	(1,185)	(97)	—	(1,282)
Payments/returns relating to sales in the prior years	—	—	—	—
Balance at December 31, 2018	592	325	334	1,251

Total revenue-related reserves for the years ended December 31, 2019 and 2018 above, included in our consolidated balance sheets, are summarized as follows:

(In thousands)	December 31, 2019	December 31, 2018
Reduction of accounts receivable	$ 540	$ 326
Component of accrued expenses	3,256	925
Total revenue-related reserves	$ 3,796	$ 1,251

The following table presents changes in our contract assets and liabilities during the year ended December 31, 2019:

(In thousands)	December 31, 2018	Additions	Deductions	December 31, 2019
Contract assets				
Accounts receivable, net [1]	$ 5,076	$ 71,542	$ (67,666)	$ 8,952

(1) Additions to accounts receivable, net relate to amounts billed to Customers for product sales and deductions primarily relate to collection of receivables during the reporting period.

The following table presents changes in our contract assets and liabilities during the year ended December 31, 2018:

(In thousands)	December 31, 2017	Additions	Deductions	December 31, 2018
Contract assets				
Accounts receivable, net [1]	$ —	$ 16,374	$ (11,298)	$ 5,076

(1) Additions to accounts receivable, net relate to amounts billed to Customers for product sales and deductions primarily relate to collection of receivables during the reporting period.

Note 11. Collaboration and License Agreements

Celgene Corporation

To date, our revenue has primarily been generated from our collaboration agreements with Celgene, or collectively, the Collaboration Agreements. Celgene is a related party through ownership of our common stock. In April 2010, we entered into a discovery and development collaboration and license agreement focused on cancer metabolism, or the 2010 Agreement. The 2010 Agreement was amended in October 2011 and July 2014. In April 2015, we entered into a joint worldwide development and profit share collaboration and license agreement with Celgene, and our wholly owned subsidiary, Agios International Sarl, entered into a collaboration and license agreement with Celgene International II Sarl, or collectively, the AG-881 Agreements, to establish a worldwide collaboration focused on the development and commercialization of vorasidenib products. The AG-881 Agreements were terminated effective September 4, 2018. In May 2016, we entered into a master research and collaboration agreement with Celgene, or the 2016 Agreement.

2016 Agreement

In May 2016, we entered into the 2016 Agreement focused on metabolic immuno-oncology, 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, 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 having the right to be the lead party for the first such program, and each party will have a 50% profit or loss share. The lead party for the United States will book commercial sales of licensed products, if any, in the United States, and Celgene will book commercial sales of licensed products, if any, outside of the United States.

License agreements

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

Financial terms

Under the terms of the 2016 Agreement, we received an initial upfront payment in the amount of $200.0 million. The 2016 Agreement provides specified rights to extend the research term for up to two, or in specified cases, up to four, additional years by paying a $40.0 million per-year extension fee. Celgene will pay an $8.0 million designation fee for each program that Celgene designates for further development and for each continuation program. During the year ended December 31, 2017, we received $8.0 million from Celgene upon the designation of AG-270 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.

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, and were subsequently terminated in September 2018 as discussed below.

Termination of AG-881 Agreements

We and Celgene terminated the AG-881 Agreements, effective as of September 4, 2018. From and after September 4, 2018, we obtained sole global rights to vorasidenib. 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 is eligible to receive royalties from us at a low single-digit percentage rate on worldwide net sales of products containing vorasidenib and (b) we and Celgene agreed to split certain agreed-upon worldwide development costs for vorasidenib until December 31, 2018. In addition, for a specified period and subject to specified exceptions, Celgene and its affiliates are prohibited from developing, manufacturing or commercializing any product that inhibits IDH1 at specified levels of binding for any indication and we are prohibited from developing, manufacturing or commercializing vorasidenib 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. On August 1, 2017, the FDA granted Celgene approval of IDHIFA® for the treatment of adult patients with R/R AML with an IDH2 mutation as detected by an FDA-approved test.

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 receive royalties at tiered, low-double digit to mid-teen percentage rates on net sales of IDHIFA®.

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 this agreement for convenience in its entirety upon ninety days written notice to us. If either party is in material breach and fails to cure such breach within the specified cure period, the other party may terminate the 2010 Agreement in its entirety. Either party may terminate the agreement in the event of specified insolvency events involving the other party.

Collaboration revenue

Performance obligations identified

Upon the adoption of ASC 606 on January 1, 2018, we applied the practical expedient that permits aggregating the effect of all contract modifications that occurred prior to January 1, 2018. No other practical expedients were used. Similar to the accounting under ASC 605-25, the 2016 Agreement was determined to be a modification of the 2010 Agreement and the AG-881 Agreements.

In determining the appropriate amount of revenue to be recognized under ASC 606, we performed the following steps: (i) identified the promised goods or services in the contract; (ii) determined whether the promised goods or services are performance obligations including whether they are distinct in the context of the contract; (iii) measured the transaction price, including the constraint on variable consideration; (iv) allocated the transaction price to the performance obligations; and (v) recognized revenue when (or as) we satisfied each performance obligation.

The transaction price is calculated as the total amount of consideration to which the Company expects to be entitled to in exchange of transferring the promised goods and services to Celgene, and excludes any amounts of variable consideration that have been constrained (being contingency based development, regulatory and sales based milestones for which the Company cannot assert it is probable that a significant reversal of cumulative revenue recognized will not occur when the uncertainty associated with the milestone is subsequently resolved). The transaction price upon the adoption of ASC 606 was comprised of all consideration received to date under the agreements, as well as the estimated amount of research and development cost reimbursements that will be received under the agreement.

The transaction price was subsequently allocated to the individual performance obligations based on their relative standalone selling prices. We developed assumptions that require judgment to determine the stand-alone selling price, or SSP, for each performance obligation identified in the contract. We use key assumptions to determine the SSP, which include forecast of

revenues, development timelines, reimbursement rates for personnel costs, discount rates and probabilities of technical and regulatory success.

The satisfied and unsatisfied performance obligations at the time of the adoption of ASC 606, each of which are considered by us to be distinct within the context of the contract, their SSP, the method of recognizing the allocated consideration, and the period through which they are expected to be recognized were as follows:

Performance Obligations	SSP	No. of Performance Obligations	Recognition Method
Fully satisfied at time of adoption			
Licenses (1)	$ 86.7 million	4	Fully satisfied; recognized upon adoption of ASC 606
Research and development services (2)	$350.7 million	10	Fully satisfied; recognized upon adoption of ASC 606
Partially satisfied at time of adoption			
Research and development services (2)	$266.6 million	6	Proportionally as services are delivered over the performance period, expected to be through September 2023 (3)

(1) The SSP was developed by probability weighting multiple cash flow scenarios using the income approach. Our management estimates within the models include the expected, probability-weighted net profits from estimated future sales, an estimate of the direct cost incurred to generate future cash flows, a discount rate and other business forecast factors. There are significant judgments and estimates inherent in the determination of the SSP of these performance obligations. These judgments and estimates include assumptions regarding future operating performance, the timelines of the clinical trials and regulatory approvals, and other factors. If different reasonable assumptions are utilized, the SSP and revenue recognized would vary.
(2) The SSP was developed using our management's best estimate of the cost of obtaining these services at arm's length from a third-party provider and using internal full time equivalent costs to support the development services.
(3) We determined that recognizing revenue on a proportional basis using the ratio of effort incurred to date compared to the total estimated effort required to complete the performance obligation best depicts the satisfaction of our obligations under the Collaboration Agreements.

Remaining performance obligations

As of December 31, 2019, the remaining performance obligations under the Celgene agreements, their SSP, the method of recognizing the allocated consideration, and the period through which they are expected to be recognized are as follows:

Performance Obligations	SSP	No. of Remaining Performance Obligations	Recognition Method
Research and development services	$175.4 million	2	Proportionally as services are delivered over the performance period

A significant portion of revenue generated from our collaboration agreements with Celgene relates to the provision of research and development services whereby revenue is recognized under an input method using the ratio of effort incurred to date compared to the total estimated effort required to complete the performance obligation. The calculation of the total estimated effort includes the total amount of forecasted costs associated with the completion of discovery, pre-clinical or clinical trials, as well as the assumed timing of these activities and estimated patient populations. Such cost estimates include forecasted direct labor and material costs, subcontractor costs, and external contract research organization costs.

As of December 31, 2019, the aggregate amount of the transaction price allocated to performance obligations that are partially unsatisfied was $70.0 million. This amount is expected to be recognized as performance obligations are satisfied through September 2023.

Revenue recognition

During the years ended December 31, we recognized the following collaboration revenue:

(In thousands)	2019	2018	2017[1]
Services performed that were considered performance obligations upon the adoption of ASC 606			
Licenses	$ —	$ 15,000	$ —
On-going research and development services	35,954	40,575	37,953
Committee participation	—	—	167
Services performed that were not considered performance obligations as of the adoption of ASC 606			
Development activities	—	1,342	—
Commercialization Activities	3,303	3,744	2,954
Total collaboration revenue - related party	39,257	60,661	41,074

(1) Amounts prior to 2018 do not reflect the impact of the adoption of Accounting Standards Update (ASU) 2014-09, Revenue from Contracts with Customers (Topic 606), in the first quarter of 2018. See Note 2. *Summary of Significant Accounting Policies* for additional information.

We also recognized certain consideration received from Celgene as a reduction of research and development expenses of zero for 2019 and 2018, respectively and $7.8 million for 2017.

The following table presents changes in our contract assets and liabilities during the year ended December 31, 2019:

(In thousands)	December 31, 2018	Additions	Deductions	December 31, 2019
Contract assets				
Collaboration receivable – related party [1]	$ 2,462	$ 8,253	$ (9,176)	$ 1,539
Royalty receivable – related party [2]	2,234	10,542	(9,876)	2,900
Contract liabilities				
Deferred revenue – related party, current and non-current portions [3]	92,519	4,948	(35,954)	61,513

(1) Additions to collaboration receivables - related party relate to amounts billed to Celgene for reimbursable costs incurred by us during the reporting period. Deductions to receivables relate to collection of receivables during the reporting period.
(2) Additions to receivables relate to amounts billed to Celgene during the reporting period. Deductions to receivables relate to collection of receivables during the reporting period.
(3) Additions to deferred revenue relate to consideration from Celgene during the reporting period. Deductions relate to deferred revenue recognized as revenue during the reporting period.

The following table presents changes in our contract assets and liabilities during the year ended December 31, 2018:

(In thousands)	December 31, 2017	Additions	Deductions	December 31, 2018
Contract assets				
Collaboration receivable – related party [1]	$ 2,448	$ 28,695	$ (28,681)	$ 2,462
Royalty receivable – related party [2]	1,222	7,087	(6,075)	2,234
Contract liabilities				
Deferred revenue – related party, current and non-current portions [3]	163,640	9,237	(80,358)	92,519

(1) Additions to collaboration receivables - related party relate to amounts billed to Celgene for reimbursable costs incurred by us during the reporting period. Deductions to receivables relate to collection of receivables during the reporting period.
(2) Additions to receivables relate to amounts billed to Celgene during the reporting period. Deductions to receivables relate to collection of receivables during the reporting period.
(3) Additions to deferred revenue relate to consideration from Celgene during the reporting period. Deductions relate to deferred revenue recognized as revenue during the reporting period and the cumulative catch-up adjustment recognized upon adoption of ASC 606 on January 1, 2018.

During the years ended December 31, 2019, 2018 and 2017, we recognized the following as revenue due to changes in the contract liability balances:

(In thousands)	2019	2018	2017[1]
Amounts included in the contract liability at the beginning of the period	$ 31,605	$ 37,590	$ —
Performance obligations satisfied in previous periods	—	469	—

(1) Amounts prior to 2018 do not reflect the impact of the adoption of Accounting Standards Update (ASU) 2014-09, Revenue from Contracts with Customers (Topic 606), in the first quarter of 2018. See Note 2. Summary of Significant Accounting Policies for additional information.

Royalty revenue

During the years ended December 31, 2019, 2018 and 2017, we recognized the following as royalty revenue:

(In thousands)	2019	2018	2017
Royalty revenue – related party	$ 10,542	$ 7,215	$ 1,937

As the underlying performance obligation, or delivery of the enasidenib license, had been satisfied as of June 2014, royalty revenue is recognized as the related sales occur.

Milestone revenue (variable consideration)

At each reporting period we evaluate whether milestones are considered probable of being reached and, to the extent that a significant reversal would not occur in future periods, estimate the amount to be included in the transaction price using the most likely amount method. Milestone payments that are not within our control, such as regulatory approvals, are not considered probable of being achieved and are excluded from the transaction price until those approvals are received.

During the year ended December 31, 2019, we did not receive any milestone payments related to our Celgene Agreements, and all variable consideration relating to the remaining development, regulatory and sales-based milestones that can be earned under the terms of the agreement remain fully constrained.

During the year ended December 31, 2018, Celgene submitted an MAA to the EMA for IDHIFA® for IDH2 mutant-positive R/R AML. As a result of the filing, we determined that a $15.0 million milestone payment for the filing of a first new drug application equivalent in an ex-U.S. country was considered probable of being reached and that a significant reversal of revenue would not occur in future periods. As the underlying performance obligation, or delivery of the license to IDHIFA®, had been satisfied as of June 2014, the milestone payment was recognized in full as collaboration revenue.

The next potential milestone expected to be achieved under our collaboration agreements with Celgene is the first regulatory approval in any of China, Japan or a major European country. Achievement of this event will result in a milestone payment of $35.0 million under the 2010 Agreement.

CStone Pharmaceuticals

In June 2018, we entered into an exclusive license agreement with CStone, or the CStone Agreement, to grant CStone specified intellectual property licenses to enable CStone to develop and commercialize certain products containing ivosidenib in mainland China, Hong Kong, Macau, and Taiwan. 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, cholangiocarcinoma, and, at our discretion, brain cancer indications.

Under the terms of the CStone Agreement, we received an initial upfront payment in the amount of $12.0 million and are entitled to receive up to an additional $407.0 million in milestone payments upon the achievement of certain development, regulatory and sales milestone events. Approximately one third of the milestone payments are related to development and regulatory milestones, half of which are related to ivosidenib in AML and cholangiocarcinoma and the other half are related to brain cancer indications, including glioma. We will also be entitled to receive tiered royalties, ranging from 15% to 19% percent, on annual net sales, if any, of ivosidenib.

CStone is responsible for all costs it incurs in developing, obtaining regulatory approval of, and commercializing ivosidenib in mainland 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 our case, in mainland China, Hong Kong, Macau, and Taiwan.

Termination

Unless earlier terminated, the CStone Agreement will expire upon the expiration of the last royalty term for the last licensed product within the scope of the CStone Agreement. At any time after CStone has obtained regulatory approval in mainland China in R/R AML and the last patient has been enrolled in a specified clinical trial (or, if earlier, at any time that CStone acquires or is acquired by an entity with a competing or restricted product), CStone may terminate the CStone Agreement in its entirety by providing us with prior written notice. Either party may, subject to specified cure periods, terminate the CStone Agreement in the event of the other party's uncured material breach. Either party may terminate the CStone Agreement under specified circumstances relating to the other party's insolvency. We have the right to terminate the CStone Agreement immediately if CStone or its affiliates or sublicensees or subcontractors challenges the validity, patentability, or enforceability of certain patent rights that relate to ivosidenib and are owned by or licensed to us or our affiliates.

Collaboration revenue

Performance obligations identified

We developed assumptions that require judgment to determine the SSP for each performance obligation identified in the contract. We use key assumptions to determine the SSP, which include forecast of revenues, development timelines, reimbursement rates, discount rates and probabilities of technical and regulatory success.

The satisfied and unsatisfied performance obligations, each of which are considered by us to be distinct within the context of the contract, their SSP, the method of recognizing the allocated consideration, and the period through which they are expected to be recognized are as follows:

Performance Obligations	SSP	No. of Performance Obligation(s)	Recognition Method
Licenses (1)	$ 16.4 million	1	Fully satisfied; recognized upon delivery of license
Other services (2)	$ 1.7 million	1	As services are delivered, expected to be through September 2021

(1) The SSP was developed by probability weighting multiple cash flow scenarios using the income approach. Our management estimates within the models include the expected, probability-weighted net profits from estimated future sales, an estimate of the direct costs incurred to generate future cash flows, a discount rate and other business forecast factors. There are significant judgments and estimates inherent in the determination of the SSP of this performance obligation. These judgments and estimates include assumptions regarding future operating performance, the timelines of the clinical trials and regulatory approvals, and other factors. If different reasonable assumptions are utilized, the SSP and revenue recognized would vary.
(2) The SSP was developed using our management's best estimate of the cost of obtaining these services at arm's length from a third-party provider.

As of December 31, 2019, the aggregate amount of the transaction price allocated to performance obligations that are partially unsatisfied was $0.4 million. This amount is expected to be recognized as performance obligations are satisfied through September 2021.

Revenue recognition

During the years ended December 31, we recognized the following collaboration revenue:

(In thousands)	2019	2018	2017
Services performed that were considered performance obligations upon contract inception			
Licenses	$ 5,000	$ 12,440	$ —
Other services	235	—	—
Services performed that were not considered performance obligations upon contract inception			
Other services	3,027	230	—
Total collaboration revenue - other	$ 8,262	$ 12,670	$ —

The following table presents changes in our contract assets during the year ended December 31, 2019:

(In thousands)	December 31, 2018	Additions	Deductions	December 31 2019
Contract assets				
Collaboration receivable – other [1]	$ 670	$ 8,262	$ (7,004)	$ 1,928

(1) Additions to contract assets relate to receivables from CStone and deductions to contract assets relate to collection of receivables during the reporting period.

The following table presents changes in our contract assets during the year ended December 31, 2018:

(In thousands)	December 31, 2017	Additions	Deductions	December 31 2018
Contract assets				
Collaboration receivable – other [1]	$ —	$ 12,670	$ (12,000)	$ 670

(1) Additions to contract assets relate to receivables from CStone and deductions to contract assets relate to collection of receivables during the reporting period.

Royalty revenue

The license was determined to be the predominant item to which sales-based royalties and sales-based milestones relate. As the license was delivered in June 2018, we will recognize royalty revenue when the related sales occur. To date, no royalties have been received under the CStone Agreement.

Milestone revenue (variable consideration)

During the year ended December 31, 2019, upon the dosing of the first patient in a local study in a hematological indication in mainland China, we earned and received a milestone payment of $5.0 million, which was recognized as collaboration revenue.

Aurigene Discovery Technologies Limited

In April 2017, we entered into a global license agreement with Aurigene Discovery Technologies Limited, or Aurigene, to research, develop and commercialize small molecule inhibitors for DHODH, or the Aurigene Agreement.

Under the terms of the Aurigene Agreement, Aurigene will provide us exclusive rights to its portfolio of novel small molecules for DHODH. Financial terms of the Aurigene Agreement include a $3.0 million upfront payment and potential future milestone payments of up to $15.0 million if we achieve certain development and regulatory milestones.

Aurigene is also eligible to receive low single-digit royalties on net product sales, if any. We will conduct preclinical studies and, if successful, fund further global research and development, as well as regulatory and commercial activities.

The term of the Aurigene Agreement will continue until the earlier of: (a) termination for convenience at our sole discretion upon 90 days prior written notice, (b) termination by either party for material breach, or (c) the expiration of the last-to-expire of all payment obligations hereunder with respect to all licensed products under the Aurigene Agreement.

Initial payment

The $3.0 million upfront payment was incurred in the year ended December 31, 2017 and recorded as research and development expense. Costs incurred and milestone payments due to Aurigene prior to regulatory approval are recognized as expenses in the period incurred. Payments due to Aurigene upon or subsequent to regulatory approval will be capitalized and amortized over the shorter of the remaining license or product patent life.

Milestone payments

During the year ended December 31, 2019, we achieved the milestone relating to the initiation of the first phase 1 clinical trial for DHODH, and we made a payment of $2.0 million.

Note 12. Common Stock

We are authorized to issue 125,000,000 shares of our common stock. Holders of common stock are entitled to one vote per share. Additionally, holders of common stock are entitled to receive dividends, if and when declared by our board of directors, and to share ratably in our assets legally available for distribution to our shareholders in the event of liquidation.

Note 13. Share-Based Payments

Stock incentive plans

In June 2013, our Board of Directors adopted and, in July 2013 our stockholders approved, the 2013 Stock Incentive Plan, or the 2013 Plan. The 2013 Plan became effective upon the closing of our initial public offering and provides for the grant of incentive stock options, non-qualified stock options, stock appreciation rights, restricted stock awards, restricted stock units, or RSUs, performance-based stock units, or PSUs, and other stock-based awards to employees, non-employees and non-employee directors. Following the adoption of the 2013 Plan, we granted no further stock options or other awards under the 2007 Stock Incentive Plan, or the 2007 Plan. Any options or awards outstanding under the 2007 Plan at the time of adoption of the 2013 Plan remain outstanding and effective. As of December 31, 2019, the total number of shares reserved under the 2007 Plan and the 2013 Plan are 9,356,754, and we had 2,127,478 shares available for future issuance under the 2013 Plan.

The 2013 Plan provides for an annual increase, to be added on the first day of each fiscal year, beginning with the fiscal year ending December 31, 2014 and continuing until the expiration of the 2013 Plan, equal to the lesser of (i) 2,000,000 shares of common stock, (ii) 4% of the outstanding shares of common stock on such date or (iii) an amount determined by our Board of Directors. On January 1, 2020, the annual increase for the 2013 Plan resulted in an additional 2,000,000 shares authorized for issuance.

Stock options

The following table summarizes the stock option activity of all stock incentive plans for the year ended December 31, 2019:

	Number of Stock Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding at December 31, 2018	5,416,069	$ 60.10	7.30	$ 27,941
Granted	1,772,485	53.79		
Exercised	(283,200)	32.69		
Forfeited/Expired	(703,869)	68.36		
Outstanding at December 31, 2019	6,201,485	$ 58.61	7.09	$ 28,528
Exercisable at December 31, 2019	3,541,821	$ 58.90	5.89	$ 25,258
Vested and expected to vest at December 31, 2019	6,201,485	$ 58.61	7.09	$ 28,528

The weighted-average grant date fair value of options granted was $36.44, $53.22 and $35.24 during the years ended December 31, 2019, 2018 and 2017, respectively. The total intrinsic value of options exercised was $6.4 million, $65.1 million and $31.5 million during the years ended December 31, 2019, 2018 and 2017, respectively.

At December 31, 2019, the total unrecognized compensation expense related to unvested stock option awards was $92.3 million, which we expect to recognize over a weighted-average period of approximately 2.54 years.

Restricted stock units

Upon vesting, each RSU entitles the holder to receive a specified number of shares of our common stock. The following table presents RSU activity for the year ended December 31, 2019:

	Number of Stock Units	Weighted-Average Grant Date Fair Value
Unvested shares at December 31, 2018	532,144	$ 75.45
Granted	505,362	54.44
Vested	(166,740)	69.58
Forfeited	(103,813)	71.34
Unvested shares at December 31, 2019	766,953	$ 63.44

As of December 31, 2019, there was approximately $28.1 million of total unrecognized compensation expense related to RSUs, which we expect to be recognized over a weighted-average period of 1.71 years.

Performance-based stock units

At the achievement of the performance-based and service-based vesting criteria, each PSU entitles the holder to receive a specified number of shares of our common stock. The following table presents PSU activity for the year ended December 31, 2019:

	Number of Stock Units	Weighted-Average Grant Date Fair Value
Unvested shares at December 31, 2018	169,031	$ 52.67
Granted	216,143	55.43
Vested	(167,031)	52.36
Forfeited	—	—
Unvested shares at December 31, 2019	218,143	$ 55.64

Stock-based compensation expense associated with these PSUs is recognized if the underlying performance condition is considered probable of achievement using our management's best estimates. As of December 31, 2019, there was approximately $1.5 million of total unrecognized compensation expense related to PSUs with performance-based vesting criteria that are considered probable of achievement, which we expect to recognize over a weighted-average period of 0.33 years, and $8.0 million of total unrecognized compensation expense related to PSUs with performance-based vesting criteria that are considered not probable of achievement.

Market-based stock units

The Company has issued certain equity awards that contain market based vesting conditions, in which shares of stock are earned at vesting based on stock price performance. The fair value of MSUs are estimated using a Monte Carlo simulation model. Assumptions and estimates utilized in the model include the risk-free interest rate, dividend yield, expected stock volatility and the estimated period to achievement of the market condition. The following table presents MSU activity for the year ended December 31, 2019:

	Number of Stock Units	Weighted-Average Grant Date Fair Value
Unvested shares at December 31, 2018	—	$ —
Granted	42,695	41.50
Unvested shares at December 31, 2019	42,695	$ 41.50

As of December 31, 2019, there was approximately $0.8 million of total unrecognized compensation expense related to MSUs, which we expect to recognize over the remaining derived service period of 0.72 years.

2013 Employee Stock Purchase Plan

In June 2013, our Board of Directors adopted, and in July 2013 our stockholders approved, the 2013 Employee Stock Purchase Plan, or the 2013 ESPP. We issued 77,981 shares and 53,255 shares during the years ended December 31, 2019 and 2018, respectively, under the 2013 ESPP. The 2013 ESPP provides participating employees with the opportunity to purchase up to an aggregate of 327,272 shares of our common stock. As of December 31, 2019, we had 82,555 shares available for future issuance under the 2013 ESPP. On January 1, 2020, the annual increase for the 2013 ESPP resulted in an additional 509,091 shares authorized for issuance.

Stock-based compensation expense

During the years ended December 31, 2019, 2018 and 2017, we recorded stock-based compensation expense for employee and non-employee stock options, RSUs, PSUs, ESPP shares and other stock-based awards. Stock-based compensation expense by award type included within the consolidated statements of operations is as follows:

(In thousands)	2019	2018	2017
Stock options	$ 48,219	$ 51,460	$ 43,997
Restricted stock units	19,079	12,032	2,858
Performance-based stock units	2,647	8,717	—
Employee Stock Purchase Plan	1,437	1,148	954
Other stock awards	991	—	—
Total stock-based compensation expense	$ 72,373	$ 73,357	$ 47,809

Expenses related to equity-based awards were allocated as follows in the consolidated statements of operations:

(In thousands)	2019	2018	2017
Research and development expense	$ 39,029	$ 41,982	$ 30,807
Selling, general and administrative expense	33,344	31,375	17,002
Total stock-based compensation expense	$ 72,373	$ 73,357	$ 47,809

No related tax benefits were recognized for the years ended December 31, 2019, 2018 and 2017.

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

	2019	2018	2017
Risk-free interest rate	2.32 %	2.71 %	2.05 %
Expected dividend yield	—	—	—
Expected term (in years)	6.06	6.06	6.05
Expected volatility	76.19 %	76.62 %	77.73 %

Expected term

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

Volatility

We use a weighted-average of expected volatility based on the volatilities of a representative group of publicly traded biopharmaceutical companies, including ourselves. The expected volatility has been determined using a weighted-average of the historical volatilities of the representative group of companies for a period equal to the expected term of the option grant.

Risk-free rate

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

Dividends

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

Forfeitures

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

Note 14. Income Taxes

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

(In thousands)	2019	2018	2017
Domestic	$ (432,535)	$ (311,159)	$ (290,423)
Foreign	21,063	(34,869)	(24,247)
Total	$ (411,472)	$ (346,028)	$ (314,670)

We did not have any provision for income taxes for the years ended December 31, 2019, 2018 and 2017.

A reconciliation of the expected income tax benefit (expense) computed using the federal statutory income tax rate to our effective income tax rate is as follows for the years ended December 31, 2019, 2018 and 2017:

	2019	2018	2017
Income tax benefit computed at federal statutory tax rate	21.0 %	21.0 %	35.0 %
State taxes, net of federal benefit	2.8 %	0.8 %	4.0 %
Change in valuation allowance	(27.2)%	(28.4)%	(19.4)%
General business credits and other credits	5.0 %	5.7 %	10.4 %
Permanent differences and other adjustments	(1.3)%	(0.7)%	— %
Incentive stock options	(0.6)%	2.2 %	0.3 %
Foreign rate differential	0.3 %	(0.6)%	(1.6)%
Impact of federal rate change	— %	— %	(28.7)%
Total	— %	— %	— %

Deferred income taxes reflect the net tax effects of temporary differences between the carrying amount of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. Significant components of our deferred tax assets and liabilities for the years ended December 31, 2019 and 2018 are as follows:

(In thousands)	2019	2018
Deferred tax assets:		
Net operating loss carryforwards	$ 294,614	$ 211,563
Deferred revenue	14,372	21,956
Tax credit carryforwards	141,219	120,605
Purchased intangible assets	14,479	3,204
Stock-based compensation	30,861	27,636
Operating lease liability	27,173	—
Deferred rent	—	4,458
Non-deductible accruals and reserves, including inventory	4,729	4,900
Total deferred tax assets	527,447	394,322
Depreciation and amortization	(2,613)	(3,569)
Operating lease right of use asset	(22,625)	—
Less: valuation allowance	(502,209)	(390,753)
Net deferred taxes	$ —	$ —

In December 2017, the Tax Cuts and Jobs Act, or TCJA, was signed into law. Among other things, the TCJA permanently lowers the corporate federal income tax rate to 21% from the existing maximum rate of 35%, effective for tax years including or commencing January 1, 2018. As a result of the reduction of the corporate federal income tax rate to 21%, U.S. GAAP requires companies to revalue their deferred tax assets and deferred tax liabilities as of the date of enactment, with the resulting tax effects accounted for in the reporting period of enactment. This revaluation resulted in a provision of $90.0 million to income tax expense in continuing operations and a corresponding reduction in the valuation allowance. As a result, there was no impact on our consolidated statements of operations from the reduction in tax rate. The other provisions of the TCJA did not have a material impact on the consolidated financial statements.

As of December 31, 2019, we had net operating loss carryforwards, or NOLs, available to reduce federal, state and foreign income taxes of approximately $1,133.0 million, $877.9 million and $61.9 million, respectively. If not utilized, these NOLs begin to expire in 2033 (for pre-2018 NOLs), 2032 and 2023, respectively. Approximately $669.6 million of federal NOLs can be carried forward indefinitely. At December 31, 2019, we also had available research and development tax credits for federal and state income tax purposes of approximately $31.2 million and $15.0 million, respectively. If not utilized, the credits begin to expire in 2027 and 2020 for federal and state income tax purposes, respectively. We engaged in clinical testing activities and incurred expenses that qualify for the federal orphan drug tax credit. At December 31, 2019, we had available orphan drug tax credits for federal purposes only of approximately $98.1 million. If not utilized, the orphan drug credits begin to expire in 2035.

As provided by Section 382 of the Internal Revenue Code of 1986, or Section 382, and similar state provisions, utilization of NOLs and tax credit carryforwards may be subject to substantial annual limitations due to ownership change limitations that have previously occurred or that could occur in the future. Ownership changes may limit the amount of NOLs and tax credit carryforwards that can be utilized annually to offset future taxable income and tax, respectively. In general, an ownership change, as defined by Section 382, results from transactions that increase the ownership of five percent stockholders in the stock of a corporation by more than 50 percent in the aggregate over a three year period. We completed a review of our changes in ownership through December 31, 2019 and determined that transactions have resulted in no ownership changes during the year ended December 31, 2019, as defined by Section 382. The impact of the historical ownership changes has been reflected in our deferred tax assets in the table above. There could be additional ownership changes after December 31, 2019 that could further limit the amount of NOLs and tax credit carryforwards that we can utilize.

As required by ASC 740, we have evaluated the positive and negative evidence bearing upon the realizability of our deferred tax assets. Based on the weight of available evidence, both positive and negative, we recorded a valuation allowance of $502.2 million and $390.8 million as of December 31, 2019 and December 31, 2018, respectively, because we have determined that it is more likely than not that these assets will not be fully realized. The valuation allowance increased by $111.4 million and $88.8 million for the years ended December 31, 2019 and, 2018, respectively.

In December 2019, the FASB issued Accounting Standards Update No. 2019-12 – *Income Taxes (Topic 740) Simplifying the Accounting for Income Taxes,* as part of its initiative to reduce complexity in the accounting standards. The amendments in ASU 2019-12 eliminate certain exceptions related to the approach for intraperiod tax allocation, the methodology for calculating income taxes in an interim period and the recognition of deferred tax liabilities for outside basis differences. ASU 2019-12 also clarifies and simplifies other aspects of the accounting for income taxes. The amendments in ASU 2019-12 are effective for the fiscal years beginning after December 15, 2020. Early adoption is permitted, including adoption in any interim period. The Company has early adopted this amendment as of January 1, 2019. There was no material impact to the Company's consolidated financial position, results of operation, or cash flows.

We apply the accounting guidance in ASC 740 related to accounting for uncertainty in income taxes. Our reserves related to taxes are based on a determination of whether, and how much of, a tax benefit taken by us in our tax filings or positions is more likely than not to be realized following resolution of any potential contingencies present related to the tax benefit.

The following table presents our unrecognized tax benefits activity for the years ended December 31, 2019 and 2018:

(In thousands)	2019	2018
Unrecognized tax benefits at the beginning of the year	$ 14,288	$ 11,263
Gross increases - current period tax positions	3,172	3,025
Unrecognized tax benefits at the end of the year	$ 17,460	$ 14,288

The uncertain tax position does not impact our effective income tax rate due to the full valuation allowance.

We are subject to taxation in the United States and Switzerland. The statute of limitations for assessment by the IRS and state tax authorities is open for tax years ending December 31, 2019, 2018, 2017, and 2016, although carryforward attributes that were generated for tax years prior to 2016 may still be adjusted upon examination by the IRS or state tax authorities if they either have been, or will be, used in a future period. The statute of limitations for assessment in Switzerland remains open for tax year ending December 31, 2019, 2018, 2017, and 2016. There are currently no federal, state or foreign audits in progress.

Note 15. Defined Contribution Benefit Plan

We sponsor a 401(k) retirement plan, in which substantially all of our full-time employees are eligible to participate. Participants may contribute a percentage of their annual compensation to this plan, subject to statutory limitations. We will make matching contributions equal to 100% of the employee's contributions, subject to a maximum of 4% of eligible compensation.

Note 16. Net Loss per Share

Basic net loss per share is calculated by dividing net loss by the weighted-average shares outstanding during the period, without consideration for common stock equivalents. Diluted net loss per share is calculated by adjusting the weighted average shares outstanding for the dilutive effect of common stock equivalents outstanding for the period, determined using the treasury stock method. For purposes of the dilutive net loss per share calculation, stock options, RSUs, PSUs and MSUs for which the performance and market vesting conditions, respectively, have been deemed probable, and 2013 ESPP shares are considered to be common stock equivalents, while PSUs and MSUs with performance and market vesting conditions, respectively, that were not deemed probable as of December 31, 2019 are not considered to be common stock equivalents.

Since we had a net loss for all periods presented, the effect of all potentially dilutive securities is anti-dilutive. Accordingly, basic and diluted net loss per share was the same for the years ended December 31, 2019, 2018 and 2017.

The following common stock equivalents were excluded from the calculation of diluted net loss per share applicable to common stockholders for the periods indicated because including them would have had an anti-dilutive effect:

	Years ended December 31,		
	2019	2018	2017
Stock options	6,201,485	5,416,069	5,577,562
Restricted stock units	766,953	532,144	125,584
Performance-based stock units	72,046	169,031	—
Employee Stock Purchase Plan shares	49,418	32,304	22,062
Total	7,089,902	6,149,548	5,725,208

Note 17. Selected Quarterly Financial Data (Unaudited)

The following table contains quarterly financial information for 2019 and 2018:

2019 (in thousands, except per share data)	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Total revenue	$ 30,227	$ 26,221	$ 26,024	$ 35,440
Loss from operations	(97,483)	(113,861)	(109,060)	(105,929)
Net loss	(93,078)	(109,871)	(106,173)	(102,350)
Net loss per share – basic and diluted	(1.59)	(1.87)	(1.81)	(1.60)

2018 (in thousands, except per share data)	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Total revenue	$ 8,762	$ 40,414	$ 15,198	$ 30,013
Loss from operations	(94,012)	(72,949)	(99,162)	(96,356)
Net loss	(90,825)	(68,745)	(94,664)	(91,794)
Net loss per share – basic and diluted	(1.63)	(1.19)	(1.63)	(1.58)

EXECUTIVE **LEADERSHIP**

Jacqualyn Fouse, Ph.D.
Chief Executive Officer

Jonathan Biller
Chief Legal Officer

Chris Bowden, M.D.
Chief Medical Officer

Bruce Car, Ph.D.
Chief Scientific Officer

Andrew Hirsch
Chief Financial Officer and
Head of Corporate Development

Melissa McLaughlin
Chief People Officer

Darrin Miles
SVP, U.S. Commercial and
Global Marketing

Orlando Oliveira
SVP and General Manager,
International

Clive Patience, Ph.D.
EVP, Technical Operations

BOARD OF **DIRECTORS**

Paul Clancy
Former EVP & CFO, Alexion

Ian Clark
Former CEO, Genentech

Kaye Foster
Former SVP Global Human
Resources, Onyx Pharmaceuticals

Jacqualyn Fouse, Ph.D
CEO, Agios

Maykin Ho, Ph.D.
Retired Partner,
Goldman Sachs Group

John Maraganore, Ph.D.
Lead Independent Director, Agios;
CEO, Alnylam Pharmaceuticals

David Scadden, M.D
Hematologist/Oncologist;
Professor, Harvard

David Schenkein, M.D
Chairman of the Board, Agios;
General Partner, GV

ANNUAL **MEETING**

The Annual Meeting of Stockholders will be held at 9:00 a.m. EDT on May 28, 2020. You may register to attend the Annual Meeting virtually via the Internet at www.proxydocs.com/AGIO, where you will be able to vote electronically and submit questions.

Independent Auditors
PricewaterhouseCoopers LLP

Investor Inquiries
Holly Manning
617-649-8600
holly.manning@agios.com

TRANSFER **AGENT**

The transfer agent is responsible, among other things, for handling stockholder questions regarding lost stock certificates, address changes, including duplicate mailings, and changes in ownership or name in which shares are held. These requests may be directed to the transfer agent at the following address:

American Stock Transfer & Trust Company, LLC
6201 15th Avenue, Brooklyn, NY 11219
www.astfinancial.com

SEC FORM **10-K**

A copy of Agios' annual report on Form 10-K filed with the Securities and Exchange Commission is available free of charge from the company's Investor Relations Department by calling 617-649-8600, sending a request by email to Holly Manning at holly.manning@agios.com or sending a written request to:

Investor Relations
Agios Pharmaceuticals, Inc.
88 Sidney Street, Cambridge, MA 02139

agios

CORPORATE HEADQUARTERS

Agios Pharmaceuticals, Inc.
88 Sidney Street
Cambridge, MA 02139-4169

www.agios.com

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