agios

RE-IMAGINING
The Other Side of Possible

A singular focus on genetically defined diseases.

Cass, Living with Sickle Cell Disease | **Tamara,** Living with PK Deficiency | **Molly,** Living with PK Deficiency

2020 ANNUAL REPORT

In late 2020, Agios announced that we will move forward with a singular focus on accelerating and expanding our genetically defined disease portfolio, including the mitapivat clinical programs and a robust pipeline of therapeutic candidates. To enable this transformation, we made the strategic decision to sell our commercial, clinical and research-stage oncology portfolio to Servier, an independent global pharmaceutical company that is committed to the cancer community and to investing in our oncology assets and our employees who support these programs.

OUR REFOCUSED THERAPEUTIC AREA IS DEFINED BY A COMBINATION OF OUR **MOST DIFFERENTIATED FOUNDATIONAL ELEMENTS**

CELLULAR METABOLISM

Cellular metabolism is a central part of our heritage and scientific competency

GENETICALLY DEFINED DISEASE

Genetically defined disease is a broad umbrella that encompasses both rare and more common diseases

WE ARE THE PIONEERING **LEADERS IN PKR ACTIVATION**

7 Years Studying PKR Activation in the Clinic

- **~190** PATIENTS TREATED
- **15** JOURNAL ARTICLES PUBLISHED
- **3** DISEASES WITH PROOF-OF-CONCEPT ACHIEVED
- **17** CLINICAL TRIALS
- **17** MEDICAL/ SCIENTIFIC COLLABORATIONS

A LOT OF FIRSTS:

- 1st GLOBAL PK DEFICIENCY REGISTRY
- 1st INTERNATIONAL PK DEFICIENCY ADVOCACY COUNCIL
- 1st HEMOLYTIC ANEMIA ADVOCACY COALITION-BUILDING
- 1st POSITIVE PHASE 3 READOUTS IN PK DEFICIENCY

FELLOW **STOCKHOLDERS**

This past year has been nothing short of *extraordinary*—for all of us. As we experience the one-year milestone of the onset of the global COVID-19 pandemic in the U.S., I want to take a moment to reflect on this past year and acknowledge the unprecedented challenges faced by our team at Agios, the patients we serve and the global community at large. I also want to shine a light on the incredible progress we've made this year, despite these unforeseen challenges.

EXTRAORDINARY CHALLENGES

In the early months of last year, it was hard to imagine that by mid-March, the entire country would be shutting down following emergency orders from local government officials. As the situation unfolded, Agios was ready. Our facilities and HR teams went above and beyond the call of duty to ensure our labs and offices remained, and continue to remain, safe for employees who need to work onsite, including providing access to testing and contact tracing. For the teams working from home, they organized personal and professional resources like webinars on avoiding burnout, access to educational materials and activities for our children, and ongoing team-building activities to adapt our culture during this time and beyond.

Already in February of 2020, on behalf of our patients, Agios assembled a cross-functional coronavirus task force. This team responded to nearly 750 inquiries from patients and healthcare providers across dozens of countries over the span of a year. For each request, the team worked tirelessly to reduce the risk to patients and burden to healthcare systems and went to great lengths to ensure patient access to our medicines despite the difficult circumstances.

Just as we were starting to adjust to a "new normal," the disparate impact of the pandemic and events across the U.S. brought into stark relief the hard work yet to be done to improve the racial and social divides in our country. To address these issues internally at Agios, we led a diversity and inclusion initiative that included speakers and workshops on valuing differences to heighten our awareness and help us learn together, and these initiatives will continue along with our commitment to creating a diverse and inclusive workplace for our employees. We are also providing educational and informational tools to our employees to heighten awareness of the facts and issues related to this topic and ways they can be a positive force for change in their communities.

In the wake of the extraordinary challenges brought on by the global pandemic and political climate, I have been overwhelmed by the generosity, determination and spirit of the Agios team in support of each other, our patients and our communities. For this reason, I find myself incredibly hopeful for the future of our country, the promise of our industry and Agios' ability to execute on our plans on behalf of patients, the latter made evident by our tremendous progress in 2020.

EXTRAORDINARY PROGRESS IN 2020

In many ways, 2020 was the year of mitapivat, our first-in-class pyruvate kinase R (PKR) activator, which anchors our genetically defined disease portfolio and is currently being evaluated across three distinct chronic hemolytic anemias: pyruvate kinase (PK) deficiency, thalassemia and sickle cell disease. Over the last year, we've reached significant milestones in the development of mitapivat, including several "firsts" for the program:

- We reported topline data from the ACTIVATE and ACTIVATE-T Phase 3 studies evaluating mitapivat in adults with PK deficiency who were not regularly transfused and those who were regularly transfused, respectively. These data support the potential for mitapivat to be the first disease-modifying therapy for PK deficiency and will be the basis for our global regulatory filing that is currently in process.
- We completed enrollment of our Phase 2 study of mitapivat in non-transfusion-dependent α- and β-thalassemia and designed two Phase 3 clinical trials, ENERGIZE and ENERGIZE-T, as part of our label-enabling pivotal program for this indication.
- We established proof-of-concept in sickle cell disease based on Phase 1 data from our CRADA with the NIH and completed U.S. and EU regulatory interactions that led to the design of a Phase 2/3 label-enabling pivotal program.
- We launched Anemia ID, a program providing no-cost genetic testing for patients with suspected hereditary anemias, including PK deficiency, in November.

In parallel, we also advanced our next-generation PKR activator, AG-946, to a first-in-human healthy volunteer trial and uncovered tremendous potential within our genetically defined diseases research portfolio that will serve as the next wave of Agios medicines.

The progress and potential of mitapivat and PK activation, and our other research programs in genetically defined diseases, led to our strategic decision to sell our commercial, clinical and research-stage oncology portfolio to Servier, a successful, patient-focused, global pharmaceutical company with a deep commitment to expanding its emerging oncology portfolio. Through this transaction, our oncology assets will continue to thrive in the hands of a capable steward with substantial resources and expertise, ultimately enabling the greatest overall positive impact for patients. The royalty on U.S. sales of TIBSOVO® and the milestone and royalty related to the U.S. approval of vorasidenib will allow our shareholders to benefit from the future success of the two most visible assets in the oncology portfolio. The $1.8 billion upfront payment provided Agios with the capital needed to accelerate the next chapter of our success with a singular focus on accelerating and expanding our genetically defined diseases portfolio, as well as the opportunity to realign our capital structure by returning $1.2 billion to shareholders in the form of share repurchases.

Embracing Our Past. **Re-imagining Our Future.**

EXTRAORDINARY OPPORTUNITIES

As we re-imagine the future of Agios, we anticipate a catalyst-rich year ahead for mitapivat across our three initial disease indications. Beyond mitapivat, Agios is advancing a growing genetically defined diseases pipeline based on our core expertise in cellular metabolism and pioneering leadership in PK activation.

Here's a quick look at what's ahead for Agios in 2021:

- File for regulatory approval for mitapivat in adults with PK deficiency in the U.S. in the second quarter of 2021 and EU in mid-2021.
- Initiate two Phase 3 studies of mitapivat — ENERGIZE and ENERGIZE-T — in not regularly transfused and regularly transfused adults with thalassemia in the second half of 2021.
- Initiate Phase 2/3 study of mitapivat in sickle cell disease by year-end.
- Prioritize new indications for PKR and pyruvate kinase M2 (PKM2) activator clinical development by year-end.

Agios is at an exciting inflection point as we prepare to move forward with a singular focus on genetically defined diseases. 2021 will be a year of significant momentum and further evidence of our potential to meaningfully impact the lives of patients with unmet needs in PK deficiency, thalassemia, sickle cell disease and other genetically defined diseases. As we re-imagine the future of Agios, we look forward to building on our core values and pioneering leadership in cellular metabolism to expand and accelerate our work on behalf of patients.

To close, I would like to thank my ***extraordinary*** Agios colleagues and collaborators for their dedication and passion for making a difference for patients — both in oncology and genetically defined diseases — even through these uncertain times. I also want to thank all of the patients, caregivers, nurses and physicians who participate in our clinical trials. Without them we could not do what we do. Finally, thank you to our founders, board members and stockholders for your continued support as we work together to achieve the other side of possible.

Jackie Fouse, Ph.D.
Chief Executive Officer

PIPELINE OVERVIEW

PRECLINICAL	EARLY STAGE CLINICAL	LATE STAGE CLINICAL	REGULATORY SUBMISSION	NEAR-TERM MILESTONES
Adult PK Deficiency (ACTIVATE and ACTIVATE-T)			NDA filing in Q2; MAA filing in mid-2021	Positive topline data reported for ACTIVATE and ACTIVATE-T
Adult Thalassemia (ENERGIZE and ENERGIZE-T)				Initiate ENERGIZE and ENERGIZE-T in 2H 2021
Sickle Cell Disease				Initiate Phase 2/3 study by YE 2021
Pediatric PK Deficiency				Finalized pivotal plan in Dec. 2020
AG-946				Enrolling healthy volunteers in Phase 1 study
Pediatric Thalassemia				Planning in process
Pediatric Sickle Cell Disease				Planning in process
	Other PKR/PKM2 development candidates			Prioritize new PKR and PKM2 indications for clinical development in 2021
	PAH			Submit IND in 2022
	BCAT-II			Lead optimization in process

~3-8K
PATIENTS IN U.S. & EU5
Pyruvate Kinase Deficiency

~18-23K
PATIENTS IN U.S. & EU5
β- and α-Thalassemia

~120-135K
PATIENTS IN U.S. & EU5
Sickle Cell Disease

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, 2020

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 has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☑

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☑

The aggregate market value of the voting and non-voting Common Stock held by non-affiliates of the registrant computed by reference to the price of the registrant's Common Stock as of June 30, 2020 (based on the last reported sale price on the Nasdaq Global Select Market as of such date) was $3,280,200,346.

As of February 18, 2021, there were 69,601,332 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 2021 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, 2020 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, "the Company," "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. Such risks and uncertainties include, among other things, the following: (i) the occurrence of any event, change or other circumstance that could give rise to the termination of the purchase and sale agreement with Servier Pharmaceuticals, LLC, or "Servier"; (ii) the failure of the Company to obtain stockholder approval for the proposed transaction with Servier or the failure to satisfy any of the other conditions to the completion of the proposed transaction; (iii) the effect of the announcement of the proposed transaction with Servier on the ability of the Company to retain and hire key personnel and maintain relationships with its customers, suppliers, advertisers, partners and others with whom it does business, or on its operating results and businesses generally; (iv) risks associated with the disruption of management's attention from ongoing business operations due to the proposed transaction with Servier; (v) the ability to meet expectations regarding the timing and completion of the proposed transaction with Servier, including with respect to receipt of required regulatory approvals; (vi) the failure of the Company to receive milestone or royalty payments under the purchase and sale agreement and the uncertainty of the timing of any receipt of any such payments; (vii) the uncertainty of the results and effectiveness of the use of proceeds from the proposed transaction with Servier; and (viii) other risks and uncertainties described in our reports and filings with the SEC, including the risks and uncertainties set forth in Item 1A under the heading Risk Factors in this Annual Report on Form 10-K, our Quarterly Report on Form 10-Q for the fiscal quarter ended on September 30, 2020 filed with the SEC on November 5, 2020 and other subsequent periodic reports we file with the SEC, which are available at www.sec.gov and the Company's website at www.agios.com. 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 timing and likelihood of the closing of the proposed sale of our oncology business to Servier and the amount of potential consideration we may receive in connection with the proposed sale;
- 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 products and product candidates targeting IDH1 or IDH2 mutations, PKR, MAT2A or DHODH, including TIBSOVO® (ivosidenib), IDHIFA® (enasidenib), vorasidenib, mitapivat, AG-270, and AG-946;
- our plans to develop and commercialize our product candidates, either alone or with partners;
- 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 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, in the first quarter of 2021;
    - the new drug application, or NDA, for mitapivat for the treatment of pyruvate kinase deficiency that we expect to submit to the FDA in the second quarter of 2021;
    - the marketing authorization application, or MAA, for mitapivat for the treatment of pyruvate kinase deficiency that we expect to submit to the European Medicines Agency, or EMA, in mid-2021;
- our strategic vision;
- 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;
- the impact of the COVID-19 pandemic on our business, operations, strategy, goals and anticipated milestones; 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 "Summary Risk Factors" and “Risk Factors” sections, 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.

This Annual Report on Form 10-K includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties. All of the market data used in this Annual Report on Form 10-K involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data. We believe that the information from these industry publications, surveys and studies is reliable. The industry in which we operate is subject to a high degree of uncertainty and risk due to a variety of important factors, including those described in the sections titled “Summary Risk Factors” and “Risk Factors.”

Summary Risk Factors

Our business is subject to a number of risks that if realized could materially affect our business, financial condition, results of operations, cash flows and access to liquidity. These risks are discussed more fully in the “Risk Factors” section of this Annual Report on Form 10-K. Our principal risks include the following:

- The proposed sale of our oncology business to Servier is subject to conditions, some or all of which may not be satisfied, or completed on a timely basis, if at all. Failure to complete, or unexpected delays in completing, the transaction or any termination of the purchase agreement with Servier could have an adverse effect on us, our financial condition and results of operations.
- The amount of consideration we will receive in the transaction with Servier is subject to various risks and uncertainties, including that we cannot predict the amount of royalty payments that we can expect to receive from Servier or whether the regulatory milestone payment will be achieved.
- We may not be able to realize the anticipated benefits of the transaction with Servier, including potentially deploying the proceeds from the transaction to expand our genetically defined disease business.
- Following the transaction with Servier, we will be a smaller, less diversified company with a more limited business concentrated on genetically defined diseases. As a result, we may be more susceptible to changing market conditions, including fluctuations and risks particular to the markets for patients with genetically defined diseases, which could adversely affect our business, financial condition and results of operations.
- We have incurred significant losses since inception. Our net losses were $327.4 million, $411.5 million and $346.0 million for the years ended December 31, 2020, 2019 and 2018, respectively. We expect to incur operating losses in the future and may never achieve or maintain profitability. As of December 31, 2020, we had an accumulated deficit of $1,843.5 million.
- The COVID-19 pandemic has and may continue to affect our ability to initiate or continue our planned, ongoing and future clinical trials, disrupt regulatory activities, disrupt our ability to maintain a commercial infrastructure for our products or have other adverse effects on our business and operations.
- If we do not successfully commercialize our approved products in indications for which they may be approved our prospects may be substantially harmed. Our ability to generate product revenue depends heavily on our successful development and commercialization of our products.
- We depend heavily on the success of our clinical product candidates, including vorasidenib, mitapivat, AG-270 and AG-946. Clinical trials of our product candidates may not be successful for a number of important reasons. If we or our collaborators are unable to commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed.

- We may not be successful in our efforts to identify or discover potential product candidates or to develop additional medicines of commercial value.
- Our approved products, or any of our product candidates that receive marketing approval in the future, may be less effective than previously believed or cause undesirable side effects that were not previously identified, which could compromise our ability, or that of any collaborators, to market the products.
- Our approved products, or any of our product candidates that receive marketing approval in the future, may fail to achieve the degree of market acceptance by physicians, patients, healthcare payors and others in the medical community necessary for commercial success.
- We face substantial competition, which may result in others discovering, developing or commercializing products before or more successfully than we do. 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.
- 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.
- The failure to maintain our current and future collaboration agreements could negatively impact our business prospects in the territory covered by the agreement.
- We currently rely, and expect to continue to rely, on third-party manufacturers for the materials and manufacture of our product candidates for preclinical and clinical testing and for commercial supply of any product candidate for which we or our collaborators obtain marketing approval. Any performance failure on the part of our existing or future third-party manufacturers could delay clinical development or marketing approval.
- 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. If we do not, or are unable to, obtain or maintain any issued patents for any of our lead product candidates, it could have a material adverse effect on our competitive position, business, financial condition, results of operations, and prospects.

Item 1. Business

General

We are a biopharmaceutical company committed to transforming 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 in the areas of genetically defined diseases, or GDDs, and, until the completion of the sale of our oncology business to Servier as described below, hematologic malignancies and solid tumors. To address our 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.

Proposed Sale of Oncology Business to Servier Pharmaceuticals, LLC (Servier)

On December 20, 2020, we entered into a Purchase and Sale Agreement, or the Purchase Agreement, with Servier. The Purchase Agreement provides for the sale of our commercial, clinical and research-stage oncology portfolio assets and pipeline, or oncology business, for a payment of $1.8 billion in cash at the closing, subject to certain adjustments for working capital of the oncology business at the closing and amounts for a representation and warranty insurance policy, and a payment of $200 million in cash, if, prior to January 1, 2027, vorasidenib is granted new drug application, or NDA, approval from the U.S. Food and Drug Administration, or FDA, with an approved label that permits vorasidenib's use as a single agent for the adjuvant treatment of patients with Grade 2 glioma that have an isocitrate dehydrogenase 1 or 2, or IDH1 or IDH2, mutation (and, to the extent required by such approval, the vorasidenib companion diagnostic test is granted an FDA premarket approval), as well as a royalty of 5% of U.S. net sales of TIBSOVO® from the close of the transaction through loss of exclusivity of TIBSOVO® and a royalty of 15% of U.S. net sales of vorasidenib from the first commercial sale of vorasidenib through loss of exclusivity of vorasidenib.

The transaction includes the proposed sale of our oncology business, including TIBSOVO®, our clinical-stage product candidates vorasidenib, AG-270 and AG-636, and our oncology research programs. Servier will also acquire our co-commercialization rights for Bristol Myers Squibb's IDHIFA®, the $25.0 million potential milestone payment, and conduct certain clinical development activities within the IDHIFA® development program.

The proposed sale has been approved by our Board of Directors. The parties' obligations to consummate the proposed sale are subject to customary conditions, including the approval of the sale by the holders of at least a majority of our outstanding shares of common stock, the expiration or termination of the applicable waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, and the receipt of required regulatory approvals in Germany.

Our Board of Directors may cause us to terminate the Purchase Agreement in order to enter into a definitive agreement relating to a superior proposal, subject to complying with certain conditions set forth in the Purchase Agreement, including giving Servier the opportunity to negotiate changes to the terms of the Purchase Agreement so that such superior proposal no longer constitutes a superior proposal. If we terminate the Purchase Agreement in order to enter into a definitive agreement with respect to a superior proposal, we may be required to pay to Servier a termination fee of $45 million prior to or concurrently with such termination.

We currently expect to complete the transaction at the end of the first quarter of or in the beginning of the second quarter of 2021, although we cannot assure completion by any particular date, if at all.

If the transaction is completed, we will no longer operate the oncology business and our Board of Directors expects to use the proceeds from the completion of the transaction to focus on advancing our GDD business and returning a significant portion of the proceeds to our stockholders. Notwithstanding this present expectation, our Board may use the proceeds of the transaction for other purposes for the benefit of us and our stockholders, and in connection therewith may find it necessary or advisable to use portions of the proceeds from the transaction for different or presently non-contemplated purposes.

The discussion of our business in his Annual Report on Form 10-K reflects our business as it exists on the date hereof and does not give effect to the proposed sale of our oncology business to Servier. If the transaction closes, we will be a smaller, less diversified company with a more limited business concentrated on GDDs. As a result, we may be more susceptible to changing market conditions, including fluctuations and risks particular to the markets for patients with GDDs, than a more diversified company, which could adversely affect our business, financial condition and results of operations. In addition, the diversification of our revenues, costs and cash flows will diminish following the transaction, such that our results of operations, cash flows, working capital and financing requirements may be subject to increased volatility and our ability to fund capital expenditures and investments or satisfy other financial commitments may be diminished.

Business Overview

Hematologic Malignancies and Solid Tumors

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 a 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 October 2020, we announced the withdrawal of the MAA based on feedback from the EMA's Committee for Medicinal Products for Human Use (CHMP) that the available clinical data from our single arm, uncontrolled Phase 1 trial did not sufficiently support a positive benefit-risk balance for the proposed indication. 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 were 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. On June 11, 2020 we sold our tiered, sales-based royalty rights on worldwide net sales of IDHIFA®, as well as our rights to receive up to $55.0 million in outstanding regulatory milestone payments from Bristol Myers Squibb, or BMS, to Royalty Pharma, or RPI, for $255.0 million. In addition, we and Celgene are currently evaluating enasidenib in the clinical trials described below.

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

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. We are currently evaluating vorasidenib in the clinical trials described below.

We are developing AG-270 for the treatment of cancers carrying a methylthioadenosine phosphorylase, or MTAP, deletion, which is present in approximately 15 percent of all cancers. AG-270 is an orally available selective potent inhibitor of methionine adenosyltransferase 2a, or MAT2A. On March 25, 2020, Celgene declined to exercise its right to opt into co-development and co-commercialization for AG-270, our MAT2A inhibitor development program, under our 2016 global research and collaboration agreement with Celgene, or the 2016 Agreement. We are currently evaluating AG-270 in a phase 1 dose-escalation and expansion trial in multiple tumor types carrying a MTAP, deletion, described below.

In the first quarter of 2020, we made the decision to cease the internal development of AG-636 for the treatment of hematologic malignancies, including lymphoma due to limited enrollment in our phase 1 trial in lymphoma. AG-636 is an inhibitor of the metabolic enzyme dihydroorotate dehydrogenase, or DHODH, licensed by us from Aurigene Discovery Technologies Limited, or Aurigene.

Genetically defined diseases

The lead product candidate in our genetically defined disease, or GDD, portfolio, mitapivat, is an activator of both wild-type and mutant pyruvate kinase-R, or PKR, 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. We are also developing AG-946, a next-generation PKR activator, for the potential treatment of hemolytic anemias and other indications.

In addition to the aforementioned development programs, we are seeking to advance a number of early-stage discovery programs in our focus areas of GDDs, malignant hematology and solid tumors 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

As part of our long term strategy, we have developed and articulated a strategic vision that delineates our expected evolution in light of our expected singular focus on accelerating and expanding our GDD business and our proposed sale of our oncology business to Servier. 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. 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.
- 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.

Specifically, our plan includes (i) obtaining regulatory approvals for mitapivat in PK deficiency, thalassemia and SCD, (ii) advancing at least five internally discovered molecules in clinical development spanning ten indications, (iii) fostering a robust research pipeline enabling us to submit IND applications every 12-24 months, and (iv) funding our operations through major catalysts as we approach cash-flow positivity without the need for additional follow-on equity offerings.

Our Guiding Principles

We are driven by a disciplined focus on developing medicines that transform the lives of patients. 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 based on our chosen focus 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 continuously 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 GDDs, hematologic malignancies, and solid tumors.

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 were governed by our 2016 Agreement, which expired in May 2020, described in more detail below.

Genetically defined diseases

GDDs range from a broad group of more than 600 rare diseases caused by mutations of single genes to conditions resulting from alterations in one or many genes (polygenic diseases) that affect up to millions of patients worldwide. In these disorders, the defect of single or multiple genes leads to a deficient expression or function in one or several gene products which collectively manifest in organ dysfunction. As these conditions are by nature congenital and frequently hereditary, they are often detected either by genetic testing or phenotypic diagnosis in newborns or in early childhood. A typical course of many such diseases is inexorable deterioration until death or to significant irreversible life-long disability and or suffering.

Many of these diseases carry severe or life-threatening features. Within this disease grouping, 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 France, Germany, Italy, Spain, United Kingdom, or the EU5. Many GDDs are likely to be under-diagnosed given the lack of available therapies or diagnostics, the rarity of the condition, or limited understanding of how the disease genetics relate to disease phenotype. Through the study or GDDs, and other conditions, it has been shown that small molecule therapies able to specifically correct genetic deficiencies and their associated organ dysfunction may have application in conditions that arise independent of patient genetics but for which identical organ dysfunction occurs. For example, a treatment for an hereditary hemolytic anemia may find direct application in the treatment of a secondarily acquired hemolytic anemia.

Current treatment options for these disorders are generally limited. Severe and sustained diet modification or nutrient supplementation can be beneficial in certain GDDs. 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. In addition, treatment of polygenic conditions such as achondroplasia by Vosoritide® and the monogenic condition, spinal muscular atrophy by gene therapy with Zolgensma® represent novel technologic approaches to addressing GDDs.

Most mutations driving GDDs are intracellular and not amenable to corrective treatment with enzyme replacement therapies. Novel technologic approaches such as gene therapy are also being tested in a minority of conditions and is a technology with limited application based on cost, complexity and patient selection factors. Despite the promising progress made for patients with a small group of these diseases, the majority of patients with GDDs have few therapeutic options, and the standard of care for many such conditions is palliative, meaning treatment of symptoms with no effect on underlying disease mechanisms. Our goal is to develop mechanistically specific, small molecule approaches with the potential to have disease modifying and long

term rather than palliative effects. We are taking a novel small molecule approach to correct the defects within diseased cells with a goal of developing transformative medicines for patients.

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

- Genetic definition of single or multiple gene sets linked to a consistent and recognizable disease phenotype;
- severe clinical presentation coupled with significant unmet medical need and evidence that disease damage while progressive is potentially reversible;
- sufficient patients to allow facile recruitment and statistical powering of prospective clinical trials; and
- a rigorous validation of the target, based upon a detailed mutational, structural, cell biological and biochemical analysis, to determine if a small molecule approach to correcting or significantly modifying the disease is both safe and feasible in newborn to elderly patients.

Precision Medicine Approach

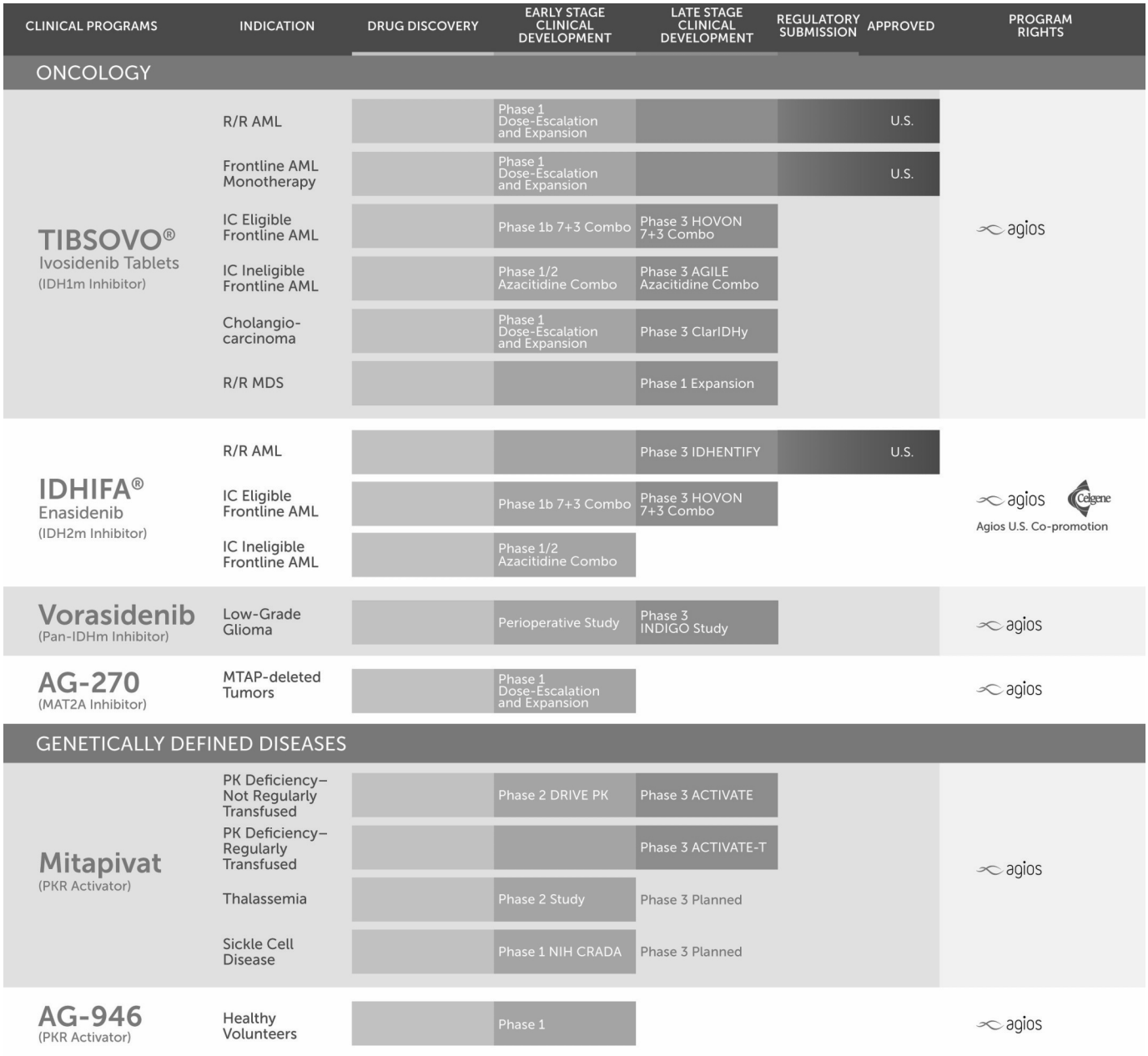
We will generally progress our drug candidates forward into phase 1 clinical trials if we have the ability to select patients who are most likely to respond to a given therapy based on biomarkers, for example, genetic or metabolic markers. To increase the probability of discovering and developing such 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 our therapeutic areas. 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, 2021, each of which is described in further detail below. As noted above, upon the completion of the sale of our oncology business to Servier we will have a singular focus on accelerating and expanding our development programs in GDDs.



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, Singapore and Taiwan to CStone, pursuant to an exclusive license agreement with CStone, or the CStone Agreement, discussed more fully below.

We are required to 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.

The FDA has approved TIBSOVO® for the treatment of adult patients with R/R AML and a susceptible IDH1 mutation and for the treatment of 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. In December 2018, we submitted a MAA to the EMA for TIBSOVO® for the treatment of adult patients with IDH1 mutant-positive R/R AML. In October 2020, we withdrew the MAA based on feedback from the EMA's CHMP that the available clinical data from our single arm, uncontrolled Phase 1 trial did not sufficiently support a positive benefit-risk balance for the proposed indication. 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. Although we experienced disruptions related to the COVID-19 pandemic, we expect to complete enrollment in 2021.
- 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, although we experienced disruptions related to the COVID-19 pandemic.
- 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 reopened enrollment of its relapsed or refractory MDS arm and although we experienced disruptions related to the COVID-19 pandemic, we expect to complete enrollment in 2021.

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 trial has completed enrollment. The primary endpoint of the trial of progression-free survival was met and, although we experienced disruptions related to the COVID-19 pandemic, we expect to file an sNDA with the FDA for TIBSOVO® in cholangiocarcinoma in the first quarter of 2021.
- A phase 1 multi-center, open-label clinical trial of ivosidenib in patients with advanced IDH1 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.

Enasidenib (mutant IDH2 inhibitor)

Celgene, pursuant to our collaboration with Celgene focused on cancer metabolism, or the 2010 Agreement, 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. The FDA has granted Celgene approval of IDHIFA® for the treatment of adult patients with R/R AML and an IDH2 mutation.

Celgene maintains worldwide development and commercial rights to enasidenib and will fund the future development and commercialization costs related to this program. Under the 2010 Agreement, we were eligible to receive royalties at tiered low-double digit to mid-teen percentage rates on any net sales of IDHIFA® and exercised our rights to provide up to one-third of the field-based commercialization efforts in the United States. On June 11, 2020, we sold our tiered, sales-based royalty rights on worldwide net sales of IDHIFA® (enasidenib), as well as our rights to receive up to $55.0 million in outstanding regulatory milestone payments from BMS, to RPI for $255.0 million. Under the 2010 Agreement, we are eligible to receive a $25.0 million potential milestone payment for the enasidenib program upon achievement of a specified ex-U.S. commercial milestone event, as well as reimbursement for costs incurred for our co-commercialization efforts and development activities.

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. In August 2020, BMS announced that the trial did not meet the primary endpoint of overall survival in patients with IDH2 mutant positive AML.

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. 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.
- The above mentioned 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, although we experienced disruptions related to the COVID-19 pandemic.

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 PK that is present in red blood cells, or RBCs. Mutations in PKR cause defects in RBC glycolysis and lead to a hematological GDD known as 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 350 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 α- and β-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-diphosphoglycerate, or 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: PKR 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 a statistically significant and clinically meaningful reduction in transfusion burden in regularly-transfused patients with PK deficiency, and we have 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. Mitapivat has been granted orphan drug designation for the treatment of PK deficiency by the FDA and the EMA. Additionally, mitapivat has received orphan drug designation from the FDA for the treatment of thalassemia and sickle cell disease.

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 regularly-transfused patients with PK deficiency. The trial has completed enrollment. Although we experienced disruptions related to the COVID-19 pandemic, we reported in January 2021 that this trial met its primary endpoint of a statistically significant and clinically meaningful reduction in transfusion burden.
- ACTIVATE, a 1:1 randomized, placebo-controlled, global, pivotal trial of mitapivat in patients with PK deficiency who do not receive regular transfusions. The trial has completed enrollment. Although we experienced disruptions related to the COVID-19 pandemic, we reported in December 2020 that this trial met its primary endpoint of a statistically significant, sustained increase in hemoglobin compared to placebo. In addition, data from the trial demonstrated that treatment with mitapivat showed statistically significant improvement in key pre-specified secondary endpoints regarding patient reported outcomes.
- A phase 2, open-label safety and efficacy clinical trial of mitapivat in adult patients with non-transfusion-dependent α- and β-thalassemia. The trial has completed enrollment.
- In collaboration with the National Institutes of Health, or NIH, we are evaluating mitapivat in a phase 1 trial in patients with sickle cell disease pursuant to a cooperative research and development agreement. The trial is ongoing and enrolling patients, although the NIH experienced disruptions related to the COVID-19 pandemic.

We anticipate filing for regulatory approval for mitapivat in adults with PK deficiency in the U.S. in the second quarter of 2021 and in the EU in mid-2021, with a potential 2022 commercial launch in both geographies. We will continue to grow our US commercial infrastructure and evaluate all options for the commercialization and continued development of mitapivat outside of the United States in order to maximize the benefit to patients and value to our shareholders, including through exploring potential partnership opportunities.

We expect to initiate two phase 3 trials of mitapivat, ENERGIZE and ENERGIZE-T, in not regularly transfused and regularly transfused adults with thalassemia in the second half of 2021.

We expect to initiate a phase 2/3 trial of mitapivat in patients with SCD by year-end 2021.

AG-946: Next-Generation PKR Activator

We are developing AG-946, a next-generation PKR activator, for the potential treatment of hemolytic anemias. We are evaluating AG-964, in a phase 1 trial of AG-946 in healthy volunteers and in patients with SCD. The trial is currently enrolling healthy volunteers, although we experienced disruptions related to the COVID-19 pandemic.

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 cancers. 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.

On April 10, 2020 Celgene notified us that they declined to elect any program as a continuation program under the 2016 Agreement. In March 2017, we previously announced that Celgene designated AG-270 as a development candidate under the 2016 Agreement and Celgene paid us an $8.0 million designation fee upon this designation. Exploratory research, drug discovery and early development of AG-270 is led by us, and Celgene had an an opt-in right on AG-270 up through phase 1 dose escalation for at least a $30.0 million fee. On March 25, 2020, Celgene declined to exercise its right to opt into co-development and co-commercialization for AG-270. As a result of these decisions we are no longer eligible for up to $168.8 million in clinical and regulatory milestone payments under the 2016 Agreement.

We are evaluating AG-270 in a phase 1 trial in multiple tumor types carrying an MTAP deletion. The first part of the trial, was a dose-escalation of AG-270 and is complete. The next part of the trial consists of two arms evaluating AG-270 in combination with taxanes. One arm of the trial 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 are enrolling patients, although we experienced disruptions related to the COVID-19 pandemic.

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 were evaluating AG-636, an inhibitor of DHODH, licensed to us from Aurigene in a phase 1 dose-escalation trial in subjects with advanced lymphomas. In the first quarter of 2020, we made the decision to halt internal development of AG-636, due to limited enrollment in this trial, and will continue to wind down the trial until the close of the proposed sale to Servier.

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.

Since December 31, 2019, there have been no material changes to the key terms of our collaboration or license agreements. For further information on the terms and conditions of our existing collaboration and license agreements, please see Item 1, *Business* included in our Annual Report on Form 10-K for the year ended December 31, 2019.

2016 Agreement

In May 2016, we entered into the 2016 Agreement focused on metabolic immuno-oncology. The initial four-year research term expired on May 17, 2020. On March 25, 2020 Celgene declined the option to extend the research agreement for up to two, or in specified cases, up to four additional one-year terms which would have required the payment of a $40.0 million extension fee. Further, on April 10, 2020 Celgene notified us that they declined to elect any program as a continuation program under the 2016 Agreement. Celgene had designated AG-270 as a development candidate under the 2016 Agreement. On March 25, 2020, Celgene notified us of their decision to decline their option to enter into a development & commercialization agreement with respect to the MAT2A program under the 2016 Agreement which would have required the payment of a $30.0 million fee to us. As a result of these decisions, the research services were fully satisfied as of May 17, 2020, no additional performance

obligations remain under the 2016 Agreement and we are no longer eligible for any milestone payments under the 2016 Agreement.

2010 Agreement

Under the 2010 Agreement, we were eligible to receive royalties at tiered low-double digit to mid-teen percentage rates on any net sales of IDHIFA® and exercised our rights to provide up to one-third of the field-based commercialization efforts in the United States. On June 11, 2020, we sold our tiered, sales-based royalty rights on worldwide net sales of IDHIFA® (enasidenib), as well as our rights to receive up to $55.0 million in outstanding regulatory milestone payments from BMS, to RPI for $255.0 million. Under the 2010 Agreement, we are eligible to receive a $25.0 million potential milestone payment for the enasidenib program upon achievement of a specified ex-U.S. commercial milestone event, as well as reimbursement for costs incurred for our co-commercialization efforts and development activities.

Further information on the terms and conditions of our existing collaboration and license agreements is included within Note 13: Collaboration and License Agreements ” of the consolidated financial statements in this Annual Report on this Form 10-K.

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, Singapore, and Taiwan, the CStone Territory, for therapeutic uses in humans, excluding brain cancer, unless added by us in our sole discretion. On March 2, 2020, we amended the CStone Agreement to include Singapore as part of the CStone Territory. 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 the Cstone Territory, 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, the CStone Territory. 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 may 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 confidential information, know-how and continuing technological innovation to develop and maintain our proprietary and intellectual property position. We may also choose to rely on trade secrets to protect certain aspects of our business that are not suitable or appropriate for patent protection.

We file, or may collaborate with third parties to file, patent applications directed to our key product candidates, including TIBSOVO® (ivosidenib), IDHIFA® (enasidenib), vorasidenib, mitapivat, AG-946, and AG-270 and AG-636, in addition to related compounds and potential back-up compounds, in an effort to establish intellectual property positions to protect these new chemical entities as well as methods of using these compounds in the treatment of diseases, formulations, solid state forms, and manufacturing processes. We may also seek patent protection for certain biomarkers that may be useful in selecting the right patient population for therapies with our product candidates. As part of our patent portfolio, as of February 1, 2021 we own or license 50 US issued patents as well as 483 issued patents in certain foreign countries and have pending patent applications in the US and in various foreign jurisdictions. The foreign issued patents and pending 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, 2021 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 patent portfolio for our IDH mutant inhibitor programs contains issued patents and pending patent applications directed to compositions of matter for our key product compounds TIBSOVO®, IDHIFA®, and vorasidenib, as well as to related compounds, methods of use, various solid state forms of these product compounds, formulations, manufacturing processes and diagnostic methods for detecting various IDH1 and/or IDH2 mutations. As of February 1, 2021, we owned approximately 38 issued U.S. patents and 310 issued foreign patents and have pending patent applications in the US and in various foreign jurisdictions. 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. In some cases, the term of a US patent can be shortened by the filing of a terminal disclaimer which operates to reduce the term of a patent to that of an earlier expiring patent.

PK activator program

The patent portfolio for our PK activator program contains issued patents and pending patent applications directed to compositions of matter for mitapivat, as well as to related compounds, various solid state forms of mitapivat, compositions of matter for second generation PKR activators, such as AG-946, as well as methods of use for these novel compounds. As of February 1, 2021, we owned approximately 6 issued U.S. patents and 128 issued foreign patents, and have pending patent applications in the US and in various foreign jurisdictions. The patents that have issued or will issue for our PK activator program will have a statutory expiration date of at least 2030 to 2040. Patent term adjustments or patent term extensions could result in later expiration dates. In some cases, the term of a US patent can be shortened by the filing of a terminal disclaimer which operates to reduce the term of a patent to that of an earlier expiring patent.

MTAP-deleted cancer program

The intellectual property portfolio for our MTAP-deleted cancer program contains issued patents and pending patent applications directed to compositions of matter for AG-270, as well as to related compounds and other chemotypes including potential back-up compounds, as well as methods of use, combination therapies, and diagnostic methods for detecting MTAP deletions. As of February 1, 2021, we owned approximately 2 issued U.S. patents and 1 issued foreign patent and have pending patent applications in the US and in various foreign jurisdictions. The patents that have issued or will issue for our MTAP-deleted cancer program will have a statutory expiration date of at least 2036 to 2040. Patent term adjustments or patent term extensions could result in later expiration dates. In some cases, the term of a US patent can be shortened by the filing of a terminal disclaimer which operates to reduce the term of a patent to that of an earlier expiring patent.

DHODH inhibitor program

The patent portfolio for our DHODH inhibitor program contains issued patents and pending patent applications, exclusively licensed to us by Aurigene, directed to compositions of matter for AG-636, as well as to related compounds and other chemotypes, as well as to methods of use for these novel compounds. The patent 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 to 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, 2021, we exclusively licensed or independently filed approximately 4 issued U.S. patents and 44 issued foreign patents and have pending patent applications in the US and in various foreign jurisdictions. 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. In some cases, the term of a US patent can be shortened by the filing of a terminal disclaimer which operates to reduce the term of a patent to that of an earlier expiring patent.

Patent Term

The term of individual patents depends upon the legal term for patents in the countries in which they are obtained. In most countries, including the United States, the patent term is 20 years from the earliest filing date of a non-provisional patent application, although term extensions may be available. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the USPTO in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier filed patent. The term of a patent that covers a drug or biological product may also be eligible for patent term extension when FDA approval is granted, provided statutory and regulatory

requirements are met. The extension of the term of foreign patents varies, in accordance with local law. Although certain of the patents granted by the regulatory authorities of the EU may expire at specific dates, the terms of patents granted in certain European countries may extend beyond such EU patent expiration date if we were to obtain a supplementary protection certificate.

In the future, if and when our product candidates receive approval by the FDA or foreign regulatory authorities, we expect to apply for patent term extensions on issued patents covering those products, depending upon the length of the clinical trials for each medicine and other factors. There can be no assurance that any of our pending patent applications will issue or that we will benefit from any patent term extension or favorable adjustment to the term of any of our patents.

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

In addition to patent protection, we also rely upon unpatented confidential information, including confidential technical information, know-how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our proprietary information, in part, by using confidentiality agreements with our collaborators, third-party service providers, scientific advisors, employees and consultants, and by 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 confidential information and know-how related to our cellular metabolism technology platform to be our primary intellectual property in this space. Confidential information and know-how can be difficult to protect. In particular, we anticipate that with respect to this technology platform, at least some of the technical information and know-how will, over time, become known within the industry through independent development, the publication of journal articles describing the methodology, and the movement of personnel skilled in the art from academic to industry scientific positions.

Competition

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

We compete in the areas of pharmaceutical, biotechnology and other related markets that address hematologic malignancies, solid tumors and GDDs. There are other companies working to develop therapies in the fields of hematologic malignancies, solid tumors and GDDs. 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., or AbbVie; Astellas Pharma Inc., or ASLAN; Bayer AG, or Bayer; BeiGene Ltd.; BMS; Clear Creek Bio; Daiichi Sankyo Company, Ltd., or Daiichi Sankyo; Eli Lilly and Company; Gilead; Forma Therapeutics Holdings, LLC, or Forma; GlaxoSmithKline plc; Jazz Pharmaceuticals plc, or Jazz; Merck & Co., or Merck; Novartis International AG, or Novartis; Pfizer, Inc., or Pfizer; and Roche Holdings, Inc., or Roche, 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 and Onureg® from BMS. Recently approved treatments for solid tumors

include Keytruda® from Merck, Rozlytrek® from Genentech 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., or IDEAYA, 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.

Genetically defined diseases. In the field of GDDs, our competitors include: Acceleron Pharma Inc., or Acceleron; BioMarin Pharmaceutical, Inc., or BioMarin; bluebird bio, Inc., or bluebird; Forma; Novartis; Pfizer; Global Blood Therapeutics, or Global Blood; IMARA Inc., or IMARA; Rocket Pharma LTD, or Rocket Pharma; and Vertex Pharmaceuticals Incorporated, or Vertex.

The most common methods for treating patients with GDDs are dietary restriction, dietary supplementation or replacement, treatment of symptoms and complications, gene therapy, blood transfusions, organ transplant and enzyme replacement therapies. There are a number of marketed therapies available for treating patients with GDDs. For example, recently-approved treatments for thalassemia, SCD, 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 GDDs. . For example, Rocket Pharma is conducting a clinical trial of a gene therapy targeting PK deficiency and Forma is developing a PKR activator for the treatment of hemolytic anemias, including PK deficiency and SCD, and Vertex is developing a gene therapy targeting 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 where appropriate, 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, AG-636 and AG-946 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, AG-636 and AG-946 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 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 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. 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, including GCP requirements, of the FDA in order to use the study as support for an IND or application for marketing approval. The GCP requirements 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. 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.

Sponsors are required to make policies for evaluating and responding to requests for expanded access for patients policies publicly available upon the earlier of initiation of a Phase 2 or Phase 3 clinical trial, or 15 days after the drug or biologic receives designation as a breakthrough therapy, fast track product, or regenerative medicine advanced therapy.

In addition to and separate from expanded access, 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 2021 is $2,875,842 for an application requiring clinical data. The sponsor of an approved NDA is also subject to an annual program fee, which for fiscal year 2021 is $336,432. 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 known as the reference listed drugs, or RLDs. Abbreviated new drug applications, or ANDAs, generally do not include preclinical and clinical data to demonstrate safety and effectiveness. Instead, the applicant may rely on the preclinical and clinical testing previously conducted for the RLD.

To approve an ANDA, 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 RLD. 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.

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

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. The FDA maintains a list of diseases that are exempt from the requirements of the Pediatric Research Equity Act, or PREA, due to low prevalence of disease in the pediatric population. Under the amended section 505B of the FDA Reauthorization Act of 2017, beginning on August 18, 2020, the submission of a pediatric assessment, waiver or deferral will be required for certain molecularly targeted cancer indications with the submission of an NDA application or supplement to an NDA application. Previously, drugs that had been granted orphan drug designation were exempt from the requirements of the PREA.

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

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 guidance also explains that a companion diagnostic device used to make treatment decisions in clinical trials of a biologic product candidate generally will be considered an investigational device, unless it is employed for an intended use for which the device is already approved or cleared. If used to make critical treatment decisions, such as patient selection, the diagnostic device generally will be considered a significant risk device under the FDA's Investigational Device Exemption, or IDE, regulations. Thus, the sponsor of the diagnostic device will be required to comply with the IDE regulations. According to the guidance, if a diagnostic device and a drug are to be studied together to support their respective approvals, both products can be studied in the same investigational study, if the study meets both the requirements of the IDE regulations and the IND regulations. The guidance provides that depending on the details of the study plan and subjects, a sponsor may seek to submit an IND alone, or both an IND and an IDE. In July 2016, the FDA issued a draft guidance document intended to further assist sponsors of therapeutic products and sponsors of *in vitro* companion diagnostic devices on issues related to co-development of these products.

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. For federal fiscal year 2021, the standard fee is $365,657 and the small business fee is $91,414. 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 2030 pursuant to the CARES Act. 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, and continue to be, 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, 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. Additionally, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the ACA-mandated "Cadillac" tax on high-cost employer-sponsored health coverage and the medical device tax and, effective January 1, 2021, also eliminated the health insurer tax. Further, the Bipartisan Budget Act of 2018, among other things, amended 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." Congress may consider other legislation to replace elements of the ACA during the next Congressional session.

The Trump Administration also took executive actions to undermine or delay implementation of the ACA. During his term, President Trump 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. On January 28, 2021, however, President Biden issued a new Executive Order which directs federal agencies to reconsider rules and other policies that limit Americans' access to health care, and consider actions that will protect and strengthen that access. Under this Executive Order, federal agencies are directed to re-examine: policies that undermine protections for people with pre-existing conditions, including complications related to COVID-19; demonstrations and waivers under Medicaid and the ACA that may reduce coverage or undermine the programs, including work requirements; policies that undermine the Health Insurance Marketplace or other markets for health insurance; policies that make it more difficult to enroll in Medicaid and the ACA; and policies that reduce affordability of coverage or financial assistance, including for dependents.

On November 10, 2020, the Supreme Court heard oral arguments as to whether 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 Tax Cuts and Jobs Act, the remaining provisions of the ACA are invalid as well. On February 10, 2021, the Biden Administration withdrew DOJ's support for this lawsuit. A ruling by the Supreme Court is expected sometime this year. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

The costs of prescription pharmaceuticals have also been the subject of considerable discussion in the United States. To date, there have been several recent U.S. congressional inquiries, as well as proposed and enacted 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. To those ends, President Trump issued five executive orders intended to lower the costs of prescription drug products but it is unclear whether, and to what extent, these orders will remain in force under the Biden Administration. Further, on September 24, 2020, the Trump Administration finalized a rulemaking allowing states or certain other non-federal government entities to submit importation program proposals to the FDA for review and approval. Applicants are 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. The FDA has 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 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.

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 Clinical Trials 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.

In January 2020, the website of the European Commission reported that the implementation of the Clinical Trial Regulation was dependent on the development of a fully functional clinical trials portal and database, which would be confirmed by an independent audit which was conducted in December 2020, and that the new legislation would come into effect six months after the European Commission publishes a notice of this confirmation. The Clinical Trial Regulation becomes applicable six months after the European Commission publishes notice of this confirmation and has published an expected system "go live" in December 2021. When the Clinical Trial Regulation becomes applicable, the existing Clinical Trial Directive and national legislation put in place to implement the Directive will be repealed. Following implementation of the Clinical Trial Regulation, a transitional period will be in effect for one year where new clinical trial applications can be submitted either under the existing Clinical Trials Directive or under the new 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 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 strict rules on the transfer of personal data to countries outside the EU, including the United States, and permits data protection authorities to impose large 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. On December 24, 2020, the United Kingdom and the European Union entered into a Trade and Cooperation Agreement, which sets out certain procedures for approval and recognition of medical products in each jurisdiction. 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 product candidates in the United Kingdom.

Furthermore, while the Data Protection Act of 2018 in the United Kingdom that "implements" and complements the EU's GDPR, is now effective in the United Kingdom, it is still unclear whether transfer of data from the European Economic Area, or EEA, to the United Kingdom will remain lawful under GDPR. The Trade and Cooperation Agreement provides for a transitional period during which the United Kingdom will be treated like an EU Member State in relation to processing and transfers of personal data for four months from January 1, 2021. This may be extended by two further months. After such period, the United Kingdom will be a "third country" under the GDPR unless the European Commission adopts an adequacy decision in respect of transfers of personal data to the United Kingdom. The United Kingdom has already determined that it considers all of the EU and EEA member states to be adequate for the purposes of data protection, ensuring that data flows from the United Kingdom to the EU and EEA remain unaffected.

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, 2020, 2019, and 2018 consisted of the following:

	2020	2019	2018
Collaboration and royalty revenues - Celgene	39 %	42 %	72 %
Collaboration revenue - CStone	2 %	7 %	13 %
Product revenue, net	59 %	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 years ended December 31, 2020 and 2019. No customers accounted for more than 10% of our consolidated revenues for year ended December 31, 2018. Refer to Note 12. *Product Revenue* and Note 13. *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
Tak W. Mak, Ph.D.	University of Toronto and the Campbell Family Institute for Breast Cancer Research
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 and Human Capital

As of December 31, 2020, we had 562 full-time employees. Of these employees, 552 were based in the United States and 10 were based in international locations and 108 held Ph.D., Pharm.D. or M.D. degrees. None of our employees are represented by a labor union or covered under a collective bargaining agreement. We also retain independent contractors to support the goals of our organization. We prioritize our employee experience and we are proud of our strong employee and contractor relations.

We understand that attracting, retaining, engaging and supporting our talented team and maintaining a diverse and inclusive organization is critical to our success and to increase the value we can provide for patients, shareholders and all stakeholders.

We strive to cultivate a positive, respectful and fair work environment guided by the following three pillars:

- Flexibility: We provide flexible work arrangements which results in happier, more engaged and more productive employees. We encourage a culture that promotes different perspectives, work styles, health and wellness, care of families and productivity.
- Psychological safety: We aim to ensure our teams experience psychological safety – the belief that risk-taking and failure will not be punished, which leads to higher performing teams, more creativity, candor and better results.
- Deliberate development: We emphasize providing ongoing opportunities for employees to grow professionally, whether through bringing in external speakers, offering preceptorships in different departments, and providing tuition reimbursement and leadership skills training.

To incentivize and reward strong performance, we have established a competitive and balanced compensation and benefits package, including short-term and long-term incentives, discretionary paid time off policy, generous parental and family leave plans and premium medical benefits.

We are committed to fostering a welcoming and diverse workplace in which individuals from a variety of backgrounds can thrive. Our diversity and inclusion program focuses on valuing three types of differences:

- Representative differences (demographic diversity, such as gender, race, ethnicity, sexual orientation)
- Experiential differences (identities based on life experiences that may change over time)
- Cognitive differences (unique ways of understanding and interpreting the world)

We are a majority female organization and we maintain significant representation at all levels, including the Board of Directors. As of December 31, 2020, 57% of our workforce were women. Racial and ethnic diversity in the aggregate has improved at our company over the last few years. As of December 31, 2020, 33% of our workforce were ethnically diverse. However, we recognize that there is still important progress to be made, particularly as relates to Black and Latino representation at our company, and this remains an area of continued emphasis for us.

We regularly evaluate the effectiveness of our human capital management practices through employee surveys and fostering a culture of ongoing feedback and two-way dialogue. In addition, we track important human capital metrics such as turnover rate. Voluntary and involuntary turnover rates across all levels (executives/ senior managers, mid-level managers and professionals) are in alignment with, or lower than, the industry average.

In 2020, the onset of the COVID-19 pandemic provided an opportunity and an imperative to demonstrate our commitment to the health and wellbeing of our employees, our patients and our community. We immediately implemented an action plan that took into consideration local and national public health guidelines and input from our employees. In response to COVID-19, we took the following actions:

- In the early stages of the pandemic, we temporarily closed our offices and labs and eliminated in-person interactions between our field staff and physicians.
- We implemented a deliberate, phased approach to returning to on-site work under a set of operating procedures designed to protect the health and wellbeing of our team and communities.
- We developed a plan for primary employees who have critical on-site work – such as those who work in our labs – to return to our Cambridge headquarters, and for our field staff to safely interact with physicians on a case-by-case basis.
- We instituted – and continue to follow – many measures to ensure the safety of those who are working on-site, including daily health screenings, requiring the use of masks, clear signage to ensure social distancing can be maintained and providing support to enable employees to commute without using public transit.
- We also partnered with Project Beacon and One Medical to facilitate regular on-site testing for employees in the office, and with Everlywell to help with testing our field-based team members for COVID-19.
- We adjusted our approach to employee communications to maintain our culture in a mostly virtual environment, such as through a dedicated intranet site (called the Stay-at-Home Hub), more frequent and virtual companywide meetings, and expanded resources such as a partnership with Out School, an online learning company, and offering LinkedIn online learning.

Throughout the pandemic, we believe our ability to embrace flexibility has helped us maintain productivity to deliver for patients.

Our Corporate Information

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 Relating to the Proposed Sale to Servier

The transaction is subject to conditions, some or all of which may not be satisfied, or completed on a timely basis, if at all. Failure to complete, or unexpected delays in completing, the transaction or any termination of the Purchase Agreement could have an adverse effect on us, our financial condition and results of operations.

The completion of the transaction is subject to a number of conditions, including the approval of the transaction by Agios stockholders and the receipt of certain regulatory approvals, which make the completion and timing of the transaction uncertain. The failure to satisfy all of the required conditions could delay the completion of the transaction for a significant period of time or prevent it from occurring at all. There can be no assurance that the conditions to the completion of the transaction will be satisfied or waived or that the transaction will be completed.

In addition, either we or Servier may terminate the Purchase Agreement under certain circumstances, including if the transaction is not completed by the outside date. In certain circumstances, upon termination of the Purchase Agreement, we would be required to pay a termination fee of $45 million to Servier.

If the transaction is not completed, we may be adversely affected and, without realizing any of the benefits of having completed the transaction, will be subject to a number of risks, including the following:

- the trading price of our common stock could decline;
- if the Purchase Agreement is terminated and our board of directors seeks another strategic transaction, our stockholders cannot be certain that we will be able to find a party willing to enter into a transaction on terms equivalent to or more attractive than the terms that Servier has agreed to in the Purchase Agreement;
- time and resources, financial and otherwise, committed by our management to matters relating to the transaction could otherwise have been devoted to pursuing other beneficial opportunities;
- we may experience negative reactions from the financial markets or from our customers, suppliers, partners or employees; and
- we will generally be required to pay our expenses relating to the transaction, such as legal, accounting and financial advisory fees, whether or not the transaction is completed.

In addition, if the transaction is not completed, we could be subject to litigation related to any failure to complete the transaction or related to any enforcement proceeding commenced against us to perform our obligations under the Purchase Agreement. Any of these risks could materially and adversely impact our business, financial condition, results of operations and the trading price of shares of our common stock.

Similarly, delays in the completion of the transaction could, among other things, result in additional transaction costs, loss of revenue or other negative effects associated with delay and uncertainty about completion of the transaction and could materially and adversely impact our business, financial condition, results of operations and the trading price of shares of our common stock.

The amount of consideration we will receive in the transaction is subject to various risks and uncertainties.

In connection with the transaction, Servier will assume certain liabilities with respect to the oncology business and pay to us:

- $1.8 billion in cash upon the completion of the transaction, subject to certain adjustments for the working capital of the oncology business at the completion of the transaction and amounts for a representation and warranty insurance policy;
- $200 million in cash if, prior to January 1, 2027, vorasidenib is granted approval for an NDA from the FDA with an approved label that permits vorasidenib's use as a single agent for the adjuvant treatment of patients with Grade 2 glioma that have an IDH1 or IDH2 mutation (and, to the extent required by such approval, the vorasidenib companion diagnostic test is granted an FDA premarket approval);
- a royalty payment of 5% of the U.S. net sales (as defined in the Purchase Agreement) of TIBSOVO® (ivosidenib) from the completion of the transaction through loss of exclusivity of TIBSOVO®; and
- a royalty payment of 15% of the U.S. net sales (as defined in the Purchase Agreement) of vorasidenib from its first commercial sale through loss of exclusivity of vorasidenib.

The consideration described above is subject to various risks and uncertainties.

The purchase price is subject to a working capital adjustment; specifically the purchase price will increase (or decrease) based on the amount of working capital of the oncology business as of the completion of the transaction relative to a specified working capital target. It is not possible to determine with precision as of the date of this Annual Report on Form 10-K the amount of working capital the oncology business may have as of the completion of the transaction and, therefore, it is possible that the working capital adjustment may result in a meaningful reduction to the base purchase price.

In addition, whether the regulatory approval milestone will be achieved prior to January 1, 2027 is subject to various risks and uncertainties, many of which are outside of the control of the parties, including adverse clinical developments with respect to vorasidenib.

Finally, the parties cannot predict what success, if any, Servier may have in the United States with respect to sales of TIBSOVO® and vorasidenib and, therefore, the amount of royalty payments that we can expect to receive from Servier under the terms of the Purchase Agreement prior to the loss of exclusivity of these products. The royalty payments are also subject to deductions and other adjustments under the terms of the Purchase Agreement, the amounts of which are uncertain as of the date of this Annual Report on Form 10-K.

The Purchase Agreement contains provisions that limit our ability to pursue alternatives to the transaction, could discourage a third party from making a favorable alternative transaction proposal, and provide that, in specified circumstances, we would be required to pay a termination fee.

The Purchase Agreement contains provisions that make it more difficult for us to be acquired by, or enter into certain strategic transactions with (including the sale of businesses to), a third party. The Purchase Agreement contains certain provisions that restrict our ability to, among other things, solicit, initiate or knowingly encourage or knowingly facilitate, or engage in or otherwise participate in any discussions or negotiations, with respect to any alternative transaction. In addition, following receipt by us of any alternative transaction proposal that constitutes a "superior proposal," Servier will have an opportunity to offer to modify the terms of the Purchase Agreement before our Board may withdraw, qualify or modify its recommendation with respect to the transaction in favor of such superior proposal.

These provisions could discourage a potential third-party acquiror that might have an interest in acquiring all or a significant portion of us or pursuing an alternative transaction from considering or proposing such a transaction.

In addition, either we or Servier may terminate the Purchase Agreement under certain circumstances, including if the transaction is not completed by the outside date. In certain circumstances, upon termination of the Purchase Agreement, we would be required to pay a termination fee of $45 million to Servier.

The pendency of the transaction, whether or not consummated, may adversely affect our business and operations.

The announcement and pendency of the transaction, whether or not consummated, may adversely affect the trading price of our common stock as well as our relationships with existing or potential suppliers, customers, vendors, distributors, licensors, licensees, collaboration partners and other business partners, and may have an adverse effect on our business, financial condition and results of operations. The pending transaction may cause such counterparties to seek to change existing business relationships with us or the oncology business, to forego new relationships or to enter into alternative agreements with our competitors because business partners may perceive that such new relationships are likely to be more stable.

In addition, our current and prospective employees, including of the oncology business, may feel uncertain about their roles with us or within the oncology business prior to and following the completion of transaction, which may have an adverse effect on our ability to attract or retain key management personnel or other key employees.

If key employees depart, our business, financial condition and results of operations may be adversely impacted.

The focus and attention of our management and employee resources may also be diverted from operational matters during the pendency of the transaction to focus on integration matters and the consummation of the transaction.

The parties must obtain certain regulatory approvals in order to complete the transaction; if such approvals are not obtained or are obtained with conditions, the transaction may be prevented or delayed or the anticipated benefits of the transaction could be reduced.

Completion of the transaction is conditioned upon the expiration or termination of the waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended. At any time before or after the transaction is completed, any of the DOJ, the FTC or U.S. state attorneys general could take action under the antitrust laws in opposition to the transaction, including seeking to enjoin completion of the transaction or condition completion of the transaction upon the divestiture of our assets, Servier or their respective subsidiaries or affiliates. Any such requirements or restrictions may prevent or delay completion of the transaction or may reduce the anticipated benefits of the transaction, which could also have an adverse effect on us, our financial condition and its results of operations.

No assurance can be given that the required regulatory approvals will be obtained or that the required conditions to closing will be satisfied, and, even if all such approvals are obtained and the conditions are satisfied, no assurance can be given as to the terms, conditions and timing of the approvals.

Lawsuits may be filed against us challenging the transaction and an adverse ruling in any such lawsuit may prevent the transaction from being completed or from being completed within the expected time frame.

One of the conditions to the completion of the transaction is the absence of any judgment or law issued or enacted by any governmental entity of competent jurisdiction, in each case that has been entered and remains and effect that prevents, enjoins, renders illegal or prohibits the consummation of the transaction. Accordingly, if litigation is filed challenging the transaction and a plaintiff is successful in obtaining an order enjoining completion of the transaction, then such order may prevent the transaction from being completed or from being completed within the expected time frame.

We may not be able to realize the anticipated benefits of the transaction.

We may not be able to realize the anticipated benefits from the transaction, including potentially deploying the proceeds from the transaction to expand its GDD business. Our ability to realize the anticipated benefits of the transaction and the success of the remaining company is subject to various risks and uncertainties, including the possibility of adverse clinical and other developments in respect of mitapivat or other pipeline products of the GDD business, the possibility that we may not be able to successfully develop and commercialize products based on PK activation and cellular metabolism and unanticipated changes in applicable laws and regulations that may adversely affect the GDD business.

We may also face new challenges operating as a smaller company as a result of the completion of the transaction, including:

- maintaining employee morale and retaining key management and other employees;
- retaining existing business and operational relationships, including with third parties, employees and other counterparties, as may be impacted by contracts containing consent and/or other provisions that may be triggered by the transaction, or with counterparties that otherwise prefer to transact with larger companies (or will only transact with smaller companies on less favorable terms); and
- raising capital on favorable terms in debt or equity markets.

Following the transaction, we will be a smaller, less diversified company.

The transaction will result in us being a smaller, less diversified company with a more limited business concentrated on GDDs. As a result, we may be more susceptible to changing market conditions, including fluctuations and risks particular to the markets for patients with GDDs, than a more diversified company, which could adversely affect our business, financial condition and results of operations. In addition, the diversification of our revenues, costs and cash flows will diminish following the transaction, such that our results of operations, cash flows, working capital and financing requirements may be subject to increased volatility and our ability to fund capital expenditures and investments or satisfy other financial commitments may be diminished.

We will have broad discretion as to the use of the proceeds from the transaction, and may not use the proceeds effectively.

We will have broad discretion with respect to the use of proceeds of the transaction. The results and effectiveness of the use of proceeds are uncertain, and we could spend the proceeds in ways that do not improve our remaining business, financial condition or results of operations. Our failure to apply these funds effectively could have an adverse effect on its business, financial condition and results of operations.

Risks Related to Our Financial Position and Need for Additional Capital

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

Since inception, we have incurred significant operating losses. Our net losses were $327.4 million, $411.5 million and $346.0 million for the years ended December 31, 2020, 2019 and 2018, respectively. As of December 31, 2020, we had an accumulated deficit of $1,843.5 million. To date, we have generated only modest revenue from sales of TIBSOVO® and prior to our sale to RPI of our royalty rights to IDHIFA®, royalties on sales of IDHIFA®. Other than the FDA approvals of TIBSOVO® (for the treatment of IDH1 mutant-positive adult patients with R/R AML or newly diagnosed AML who are at least 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy) and IDHIFA® (for the treatment of IDH2 mutant-positive adult patients with R/R AML), we have not obtained marketing approval for any of our product candidates, all of which are in preclinical or clinical development stages. We have financed our operations primarily through public offerings of our common stock and our collaboration agreements with Celgene and 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 as 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;
- continue our research and preclinical development of our product candidates and 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;
- add additional personnel to support our product research and 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 any of 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. We expect that our existing cash, cash equivalents and marketable securities as of December 31, 2020, together with anticipated product revenue, anticipated interest income and anticipated expense reimbursements under our collaboration and license agreements, but excluding any additional program-specific milestone payments or the anticipated proceeds from the proposed sale of our oncology business to Servier, will enable us to fund our operating expenses and capital expenditure requirements to the end of 2022. Following the completion of the transaction with Servier and the subsequent shareholder returns, we expect to have sufficient capital to fund operations through major catalysts and to cash-flow positivity without the need to raise additional equity. 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 timing and likelihood of the closing of the sale of our oncology business to Servier and the amount of potential consideration we receive in connection with the sale;
- 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;
- levels of product revenue from sales of approved medicines;
- the cost associated with preparation for the potential commercial launch of one or more of our product candidates;
- our ability to establish and maintain additional collaborations on favorable terms, if at all;
- our ability to successfully execute on our strategic plans;

- operational delays due to the COVID-19 pandemic; and
- the extent to which we acquire or in-license, or monitor or out-license, other medicines and technologies.

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 as we can generate positive cash flow, we expect to finance our cash needs through a combination of cash on hand, equity offerings, debt financings, collaborations, strategic alliances, licensing arrangements and other nondilutive strategic transactions. We do not have any committed external source of funds, other than agreements with our collaborators, which are limited in scope and duration. To the extent that we raise additional capital from the issuances and sales of our common stock pursuant to the 2020 sales agreement or through the sale of equity or convertible debt securities, the ownership interests of our common 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 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. For example, in June 2020 we sold our tiered, sales-based royalty rights on worldwide net sales of IDHIFA®, as well as our rights to receive up to $55.0 million in outstanding regulatory milestone payments from BMS to RPI for $255.0 million.

Changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition.

Changes in tax law may adversely affect our business or financial condition. On December 22, 2017, the U.S. government enacted the Tax Cuts and Jobs Act, or the Tax Act, which significantly reformed the U.S. Internal Revenue Code of 1986, as amended, or the Code. The Tax Act, among other things, contained significant changes to corporate taxation.

As part of Congress' response to the COVID-19 pandemic, the Families First Coronavirus Response Act, or FFCR Act, was enacted on March 18, 2020, the Coronavirus Aid, Relief, and Economic Security Act, or CARES Act, was enacted on March 27, 2020, and COVID-19 relief provisions were included in the Consolidated Appropriations Act, 2021, or CAA, which was enacted on December 27, 2020. All contain numerous tax provisions. Regulatory guidance under the Tax Act, the FFCR Act, the CARES Act, and the CAA is and continues to be forthcoming, and such guidance could ultimately increase or lessen impact of these laws on our business and financial condition. It is also possible that Congress will enact additional legislation in connection with the COVID-19 pandemic, some of which could have an impact on our company. In addition, it is uncertain if and to what extent various states will conform to the Tax Act, the FFCR Act, the CARES Act, or the CAA.

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

If we do not successfully commercialize our approved products in indications for which they may be approved our prospects may be substantially harmed.

Until the completion of the proposed sale of our oncology business to Servier, 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® could be unsuccessful if:

- the medical community and third-party payors no longer accept TIBSOVO® as safe, efficacious, and cost-effective;
- 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, or cGMP;
- we fail to successfully obtain third party reimbursement and generate commercial demand that results in sales of TIBSOVO®;
- our efforts to commercialize TIBSOVO® are impeded by the effects of the COVID-19 pandemic;
- 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;
- we fail to gain and/or maintain sufficient market acceptance by physicians, patients, healthcare payors and others in the medical community; or,
- 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 currently approved indications.

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

We may not be successful in our efforts to identify or discover potential product candidates or to develop additional medicines of commercial value and we may not achieve our goals included in our strategic vision.

A key element of our strategy has been 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 GDDs, 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 in our therapeutic areas. In addition, 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, or any medicines we develop do not effectively correct metabolic pathways or alter the metabolic state of immune cells, we will not be able to achieve our strategic vision and our specific long-term goals and will not be able generate incremental product revenue in future periods, which likely would result in significant harm to our financial position and adversely impact our stock price.

The COVID-19 pandemic has and may continue to affect our ability to initiate or continue our planned, ongoing and future clinical trials, disrupt regulatory activities, disrupt our ability to maintain a commercial infrastructure for our products or have other adverse effects on our business and operations. In addition, this pandemic may continue to adversely impact economies worldwide, which could result in adverse effects on our business and operations.

The COVID-19 pandemic, which began in December 2019, has spread worldwide, causing many governments to implement measures to slow the spread of the outbreak through quarantines, strict travel restrictions, heightened border scrutiny, and other measures. The outbreak and government measures taken in response have also had a significant impact, both direct and indirect, on businesses and commerce, as worker shortages have occurred; supply chains have been disrupted; facilities and production have been suspended; and demand for certain goods and services, such as medical services and supplies, has spiked, while demand for other goods and services, such as travel, has fallen. The future progression of the pandemic and its effects on our business and operations are uncertain.

In response to the COVID-19 pandemic, we were required to close our facilities except for a limited number of essential facilities and laboratory staff. We recently opened our Cambridge office to an additional, limited number of employees who prefer to work onsite, and our field-based employees engage with healthcare providers and other third parties remotely and, where local regulations allow, on a limited in-person basis. In the event of a continuation of shelter-in-place orders and/or other mandated local travel restrictions, our employees conducting research and development activities may not be able to access our research space, and our core activities may be significant limited or curtailed, possibly for an extended period of time. In light of the pandemic, we may choose to pause certain research programs, delay the start of certain longer-term clinical trials and limit hiring.

We may face disruptions that may affect our ability to initiate and complete clinical trials including disruptions in procuring items that are essential for our research and development activities, including, for example, raw materials used in the manufacturing of our product candidates and laboratory supplies for planned and ongoing clinical trials, in each case, for which there may be shortages because of ongoing efforts to address the outbreak. We have enrolled, and seek to enroll, patients in our clinical trials at sites located both in the United States and internationally. Site initiation, participant recruitment and enrollment, participant dosing, distribution of clinical trial materials, study monitoring and data analysis has been and may continue to be paused or delayed due to changes in hospital or university policies, federal, state or local regulations, prioritization of hospital

resources toward pandemic efforts, or other reasons related to the pandemic. We have faced and expect to continue to face difficulties recruiting or retaining patients in our ongoing clinical trials because of the pandemic. Patients enrolled in our clinical trials may be unable or unwilling to visit clinical trial sites which may impact the collection of important clinical trial data and has, and may continue to, necessitate remote data verification. In addition limitations in the ability to visit sites has affected, and may continue to adversely affect, our enrollment timelines for our clinical trials, and may adversely affect the timing of completion of our clinical trials or our ability to complete clinical trials in a fully compliant manner. For example, due to disruptions related to the COVID-19 pandemic, we have delayed our expectations for completion of enrollment of our phase 3 AGILE clinical trial and the MDS arm of our phase 1 clinical trial of ivosidenib until 2021. Additionally, the potential suspension of clinical trial activity at clinical trial sites may have an adverse impact on our clinical trial plans and timelines.

We have faced and may continue to face disruptions in our ability to prepare and submit applications to regulatory authorities for drug approvals and to build and maintain a commercial infrastructure for our products and product candidates. For example, we plan to submit to the FDA an sNDA for TIBSOVO® for previously treated IDH1 mutant-positive cholangiocarcinoma in the first quarter of 2021, which we originally intended to submit in the fourth quarter of 2020. We may face manufacturing disruptions or disruptions related to the ability to obtain necessary institutional review board or other necessary site approvals, as well as other delays at clinical trial sites.

The response to the COVID-19 pandemic may redirect resources with respect to regulatory and intellectual property matters in a way that would adversely impact our ability to progress regulatory approvals and protect our intellectual property. In addition, we may face impediments to regulatory meetings and approvals due to measures intended to limit in-person interactions.

The COVID-19 pandemic may continue to significantly impact economies and financial markets worldwide, which could result in adverse effects on our business and operations, impact our ability to raise additional funds through public offerings and impact the volatility of our stock price and trading in our stock. We cannot be certain what the overall impact of the COVID-19 pandemic will be on our business and it has the potential to adversely affect our business, financial condition, results of operations, and prospects.

We depend heavily on the success of our clinical product candidates. Clinical trials of our product candidates may not be successful for a number of important reasons. 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.

Our ability to generate product revenue will depend heavily on the successful clinical development and eventual commercialization of our current and any future 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 in foreign jurisdictions. Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans.

Clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to outcome. 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. Moreover, we, or any collaborators, may experience any of a number of possible unforeseen adverse events in connection with clinical trials, many of which are beyond our control, including:

- we, or our collaborators, may fail to demonstrate efficacy in a clinical trial or across a broad population of patients;
- 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. For example, many compounds that initially showed promise in earlier stage testing for treating cancer, GDDs or other diseases have later been found to cause side effects that prevented further development of the compound;
- our product candidates may have undesirable side effects or other unexpected characteristics or otherwise expose participants to unacceptable health risks, causing us, our collaborators or our investigators, regulators or institutional review boards or the data safety monitoring board for such trial to halt, delay, interrupt, suspend or terminate the trials or cause us, or any collaborators, 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;

- if our product candidates have undesirable side effects, it could result in a more restrictive label, such as the "black box" warning for differentiation syndrome on the labels for IDHIFA® and TIBSOVO®, or it could result in the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities;
- 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;
- 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;
- 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 GDD 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;
- significant preclinical study or clinical trial delays 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;
- the cost of clinical trials of our product candidates may be greater than anticipated; and,
- 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.

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.

Our failure to successfully begin and 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 could result in additional costs to us, or any collaborators, would impair our ability to generate revenue from product sales, regulatory and commercialization milestones and royalties and would significantly harm our business.

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. For example, in the first quarter of 2020, we made the decision to halt internal development of AG-636 for the treatment of hematologic malignancies, including lymphoma due to limited enrollment in our phase 1 trial in lymphoma. Furthermore, enrollment has been and may continue to be particularly challenging in light of the ongoing COVID-19 pandemic and even more so for some of the orphan diseases we target in our GDD programs. For example, due to disruptions related to the COVID-19 pandemic, we delayed our expectations for completion of enrollment of our phase 3 AGILE clinical trial and the MDS arm of our phase 1 clinical trial of ivosidenib until 2021.

Patient enrollment is also affected by other factors including:

- prevalence and 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 addition, some of our competitors may have ongoing or planned 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. For example, Daiichi Sankyo Company, Ltd., or Daiichi Sankyo, 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; Rocket Pharma LTD, or Rocket Pharma, developing a gene therapy targeting PK deficiency; Vertex is developing a gene therapy targeting SCD; Forma is developing a PKR activator for the treatment of hemolytic anemias, including PK deficiency and SCD; and IDEAYA Biosciences, Inc., or IDEAYA, is developing a MAT2A inhibitor for the treatment of MTAP-deleted cancers. Competition for eligible 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.

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

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 Abbott Laboratories for the development of the FDA approved diagnostic for TIBSOVO®, and may in the future depend on other third parties for the development of other companion diagnostics for our cancer therapeutic product candidates. If we or our collaborators 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.

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.

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.

Our approved products, or any of our product candidates that receive marketing approval in the future, may fail to gain and/or maintain sufficient market acceptance by physicians, patients, healthcare payors and others in the medical community. 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 approved medicines 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.

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. Potential competitors include major pharmaceutical companies, specialty pharmaceutical companies, biotechnology companies, 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. 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, high risk myelodysplasia, PK deficiency, thalassemia and SCD. For example, BMS, Jazz Pharmaceuticals plc, AbbVie Inc. (in collaboration with Roche Holdings Inc.), Novartis International AG, or Novartis, Pfizer, Inc., or Pfizer, and Astellas Pharma Inc. are each marketing therapies to treat AML, Acceleron Pharma Inc. and bluebird bio, Inc., or bluebird, are each marketing therapies to treat beta thalassemia, Novartis and Global Blood Therapeutics are each marketing therapies to treat SCD, Rocket Pharma is conducting a clinical trial of a gene therapy targeting PK deficiency, 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 GDDs.

We are developing most of our initial product candidates for the treatment of various types 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 GDDs. There are a variety of treatment options available, including a number of marketed enzyme replacement therapies, for treating patients with GDDs. In addition to currently marketed therapies, there are also a number of products that are either enzyme replacement therapies, gene therapies or PK activators in various stages of clinical development to treat GDDs. These products in development may provide efficacy, safety, convenience and other benefits that are not provided by currently marketed therapies or for which there are no approved treatments. 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 GDDs by targeting similar mechanisms of action as our product candidates. These companies include large pharmaceutical companies, such as Bayer, Daiichi Sankyo, Eli Lilly and Company, GlaxoSmithKline plc, and Merck, as well as biotechnology companies of various sizes, such as bluebird, Forma, IDEAYA, IMARA, Rocket Pharma, and Vertex. In addition, there are several companies developing immunotherapies, including metabolic immunotherapies, targeting cancer, including AstraZeneca plc; BeiGene, Ltd.; Bristol-Myers Squibb Company; GlaxoSmithKline plc; Genentech Inc.; 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.

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

- decreased demand for any product candidates or medicines that we may develop, reputational harm and lost revenue.

Although we maintain product liability insurance coverage, it may not be adequate to cover all liabilities that we may incur.

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 incidents 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 incidents 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 applies to all member states of the European Economic Area, or EEA. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data. The GDPR imposes significant obligations on us with respect to clinical trials conducted in the EEA. 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, 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 are applicable to our activities, and a wide 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 went into effect on January 1, 2020, is creating similar risks and obligations as those created by GDPR, though the California Consumer Privacy Act does exempt certain information collected as part of a clinical trial subject to the Federal Policy for the Protection of Human Subjects (the Common Rule). 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, government 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 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 that 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 collaborations for the development and commercialization of our product candidates with large and mid-size pharmaceutical companies and biotechnology companies. We face significant competition in seeking appropriate collaborators. Collaborations are complex and time-consuming to negotiate and document. 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. We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all.

If we enter into any such arrangements with collaborators, 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, 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, in March 2020, Celgene notified us of its decision to decline its option to enter into a development and commercialization agreement with respect to MAT2A and provided notice of its decision to decline its right to extend the research term of the 2016 Agreement. Further, in April 2020, Celgene notified us that BMS has declined to elect any program for continued development and opt-in rights under the 2016 Agreement.
- 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, 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 may have rights that restrict us from entering into future agreements on certain terms with potential collaborators. 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.
- 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, 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, as a result of which we became responsible for future development costs of vorasidenib.
- 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.

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. Until the completion of the sale of our oncology business to Servier, our ability to generate royalty and milestone revenue under the CStone Agreement is dependent on CStone's performance of its obligations under the CStone 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;
- There may be disputes between CStone and us, including disagreements regarding the CStone Agreement and as to future development plans, 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;
- Business combinations, significant changes in CStone's business strategy, or the impact of public health epidemics, such as the COVID-19 pandemic, may adversely affect CStone's ability or resources available to perform its obligations under the CStone Agreement; and,
- 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.

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 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 similar 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. 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 such challenges or delays that could have a material adverse impact on our business, financial condition and prospects.

Our reliance on third parties for research and development activities reduces our control over these activities but does 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 a given regulatory authority will determine that any of our clinical trials comply with cGCP regulations. 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, 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.

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 for commercialization.

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

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 respect to other product candidates 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, quality assurance, environmental and safety and pharmacovigilance reporting;
- the possible breach of the manufacturing agreement by the third party; and
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

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.

We have been monitoring our supply chain network for any disruptions due to the COVID-19 pandemic, and our manufacturers have remained largely unaffected, with any campaign delays experienced to date being limited to a few days in duration. Although global shipping continues to be disrupted due to the pandemic, we have not yet experienced a supply impact and we have accrued additional stock of TIBSOVO® in order to further mitigate risk. If either we or any third parties on which we rely are adversely impacted by restrictions resulting from the COVID-19 pandemic, our supply chain may be disrupted, limiting our ability to manufacture our product candidates for our clinical trials and research and development operations.

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 in which we intend to commercialize but we continue to actively pursue patent protection for our assets around the world.

The patent prosecution process is costly 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 and/or file patent applications on every aspect of our research and development output that is or may be eligible for patent protection. Although we enter into non-disclosure and confidentiality agreements with parties who may 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. There is also the possibility that loss or theft of data or records may jeopardize the ability to seek patent protection or impede the progress or drafting of patent applications.

We have licensed patent rights, and in the future may license additional patent rights, from third parties. Such licenses may be accompanied by milestone and/or royalty payment obligations. 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 pre-issuance 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 the patent or in one or more patent claims being narrowed or invalidated, 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 significant amount of time required for the discovery, development, preclinical and clinical testing and regulatory review and approval 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. In such circumstances we would be relying primarily on regulatory or marketing exclusivity to exclude others from commercializing a generic version of our products.

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.

The biotechnology and pharmaceutical industries are characterized by extensive litigation regarding patents and other intellectual property rights. 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. 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 opposition, derivation, revocation, reexamination, post-grant and inter partes review or interference proceedings before the USPTO or other patent offices around the world. 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 organization.

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 confidential information related to our proprietary platforms and technology, our business and competitive position could be harmed.

In addition to seeking patents for some of our technology and medicines, we also rely on maintaining the confidentiality of unpatented know-how, technology and other proprietary information, to maintain our competitive position. For example, we consider the confidential information and know-how related to our cellular metabolism technology platform to be our primary intellectual property assets in this space. Unpatented proprietary technical information and know-how can be difficult to protect.

We seek to protect this proprietary technical information and know-how, 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, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated proprietary information is difficult, expensive and time-consuming, and the outcome is unpredictable. If any of our proprietary technical information and know-how 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. Moreover, we anticipate that with respect to this platform, at least some of this technical information 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.

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 the FDA approvals 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.

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 FDA, EMA and other foreign regulatory authorities have substantial discretion in the approval process. Accordingly, it is possible that the FDA or EMA may refuse to accept for substantive review any NDA, sNDA or MAA that we submit for our product candidates, or may conclude after review of our data that our marketing 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, the applicable regulator may require that we conduct additional clinical trials, preclinical studies or manufacturing validation studies and submit that data before reconsidering our applications. Depending on the extent of these or any other FDA- or EMA-required trials or studies, approval of any marketing applications that we submit may be delayed by several years, or may require us to expend more resources than we planned. 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 any marketing applications. For example, Celgene submitted an MAA to the EMA for IDHIFA® for IDH2 mutant-positive AML which it subsequently withdrew in December 2019, and we submitted an MAA to the EMA for TIBSOVO® for the treatment of adult patients with IDH1 mutant-positive R/R AML, which we subsequently withdrew in October 2020. Celgene or we may not be successful in obtaining EMA approval of IDHIFA® or TIBSOVO®, respectively, on a timely basis, or ever. We have 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, and failure to obtain marketing approval for our products or product candidates will prevent us from commercializing the product or product candidate in the applicable jurisdictions.

Further, 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. 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.

In addition, the COVID-19 pandemic may continue to disrupt the U.S. and international healthcare and regulatory systems. These disruptions could materially delay the review of, and/or decision making with respect to, marketing approvals for our product candidates. Any delay in regulatory review or decision making resulting from such disruptions could materially affect the development of our product candidates.

Disruptions at the FDA and other agencies may prolong the time necessary for regulatory submissions to be reviewed and/or new drugs to be approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical employees and stop critical activities. If a prolonged government shutdown were to occur, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. The Trump Administration also took several executive actions that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities.

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 and any of our medicines that are approved for marketing in such jurisdiction will be subject to risk associated with foreign operations.

In order to market and sell our medicines in the EU and many other foreign 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. 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, we could face heightened risks with respect to seeking marketing approval in the United Kingdom as a result of the recent withdrawal of the United Kingdom from the EU on December 31, 2020, commonly referred to as Brexit. On December 24, 2020, the United Kingdom and EU entered into a Trade and Cooperation Agreement, which sets out certain procedures for approval and recognition of medical products in each jurisdiction. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing any 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 any product candidates, which could significantly and materially harm our business.

We expect that we will be subject to additional risks in commercializing any of our product candidates that receive marketing approval outside the United States, including 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; and workforce uncertainty in countries where labor unrest is more common than in the United States.

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.

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. The FDA may 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.

Any product or 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 or 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 market our medicines for uses other than their respective 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.

Our relationships with healthcare providers, physicians and third-party payors are 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;
- 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.

Even if we or any collaborators are able to commercialize any product candidates, such products may become subject to unfavorable pricing regulations and third-party reimbursement practices, 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. 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.

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.

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.

Current and future healthcare reform legislation may increase the difficulty and cost for us and any collaborators to obtain reimbursement and commercialize our drug candidates.

In the United States and foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability, or the ability of any collaborators, to profitably sell any product 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 products. If reimbursement of our products is unavailable or limited in scope, our business could be materially harmed.

In March 2010, President Obama signed into law the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the ACA. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. This legislation resulted in aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which will remain in effect through 2030 under the CARES Act. The American Taxpayer Relief Act of 2012, among other things, reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These 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.

Since enactment of the ACA, there have been, and continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, in 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. On

November 10, 2020, the Supreme Court heard oral arguments as to whether 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 Tax Cuts and Jobs Act, the remaining provisions of the ACA are invalid as well. On February 10, 2021, the Biden Administration withdrew the federal government's support for overturning the ACA. A ruling by the Supreme Court is expected sometime this year.

The Trump Administration also took executive actions to undermine or delay implementation of the ACA, including directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On January 28, 2021, however, President Biden issued a new Executive Order which directs federal agencies to reconsider rules and other policies that limit Americans' access to health care, and consider actions that will protect and strengthen that access. This Executive Order also directs the U.S. Department of Health and Human Services to create a special enrollment period for the Health Insurance Marketplace in response to the COVID-19 pandemic. We cannot predict how federal agencies will respond to such Executive Orders.

The costs of prescription pharmaceuticals in the United States and foreign jurisdictions is subject to considerable legislative and executive actions and could impact the prices we obtain for our drug products, if and when approved.

The costs of prescription pharmaceuticals have also been the subject of considerable discussion in the United States.

To date, there have been several recent U.S. congressional inquiries, as well as proposed and enacted 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 products. To those ends, President Trump issued several executive orders intended to lower the costs of prescription drug products. Certain of these orders are reflected in recently promulgated regulations, including an interim final rule implementing President Trump's most favored nation model, but such final rule is currently subject to a nationwide preliminary injunction. It remains to be seen whether these orders and resulting regulations will remain in force during the Biden Administration. Further, on September 24, 2020, the Trump Administration finalized a rulemaking allowing states or certain other non-federal government entities to submit importation program proposals to the FDA for review and approval. Applicants are 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. The FDA has 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.

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 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.

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. We cannot predict the likelihood, timing or effect of future transitions among our executive leadership.

Recruiting and retaining qualified scientific, clinical, manufacturing, regulatory 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 and universities and research institutions for similar personnel. Our consultants and advisors, including our scientific co-founders, who assist us in formulating our research and development and commercialization strategy 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. We also cannot be sure of the effect the announcement of our proposed sale of our oncology business to Servier will have on our ability to retain and hire key personnel. Our current and prospective employees, including of the oncology business, may feel uncertain about their roles with us or within the oncology business prior to and following the completion of transaction, which may have an adverse effect on our ability to attract or retain key management personnel or other key employees. Furthermore, the ongoing COVID-19 pandemic and our associated work from home policy may make it difficult for us to maintain our corporate culture.

We expect to continue to experience growth in the number of our employees as we expand our development, regulatory and future sales and marketing capabilities. 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. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

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 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.

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 $27.77 per share to $138.85 per share. The stock market in general and the market for biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. While the full extent of the economic impact and the duration of the

COVID-19 pandemic may be difficult to assess or predict, it has already caused, and is likely to result in further, significant disruption of global financial markets, which may reduce our ability to access capital either at all or on favorable terms.

The market price for our common stock may be influenced by many factors, including:

- perceived likelihood of the consummation of our proposed sale of our oncology business to Servier;
- 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, including shares issuable upon exercise of outstanding stock options and upon vesting of stock units under our stock incentive plans;
- variations in our financial results, including fluctuations in levels of sales of TIBSOVO® or results of companies that are perceived to be similar to us;
- whether an active trading market for our shares is sustained;
- changes in estimates, evaluations or recommendations by securities analysts, that cover our stock or the failure by one or more securities analysts to continue to cover our stock;
- changes in the structure of healthcare payment systems;
- the societal and economic impact of public health epidemics, such as the ongoing COVID-19 pandemic and any recession, depression or sustained market event resulting from the pandemic;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions; and
- the other factors described in this "Risk Factors" section.

In the past, following periods of volatility in the market price of a companies 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 managements attention and resources, which could seriously harm our business, financial condition, results of operations and prospects.

We also cannot guarantee that an active trading market for our shares will be sustained. An inactive trading market for our common stock may 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.

Our financial condition and operating results also may fluctuate 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.

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

As of December 31, 2020, our executive officers, directors and principal 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 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 Code and corresponding provisions of state law, if a company undergoes an "ownership change," generally defined as a greater than 50% change (by value) in its equity ownership by certain stockholders over a three-year period, the company'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 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. 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.

There is also a risk that due to regulatory changes, such as suspensions on the use of net operating losses, or other unforeseen reasons, our existing net operating losses could expire or otherwise become unavailable to offset future income tax liabilities. The Tax Act, as amended by the CARES Act, includes changes to U.S. federal tax rates and the rules governing net operating loss carryforwards that may significantly impact our ability to utilize our net operating losses to offset taxable income in the future. In addition, state net operating losses generated in one state cannot be used to offset income generated in another state. For these reasons we may be unable to use a material portion of our net operating losses and other tax attributes.

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 from previous periods or our current expectations due to numerous factors, including as a result of 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 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. 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, 2020, 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 18, 2021, there were approximately 11 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.

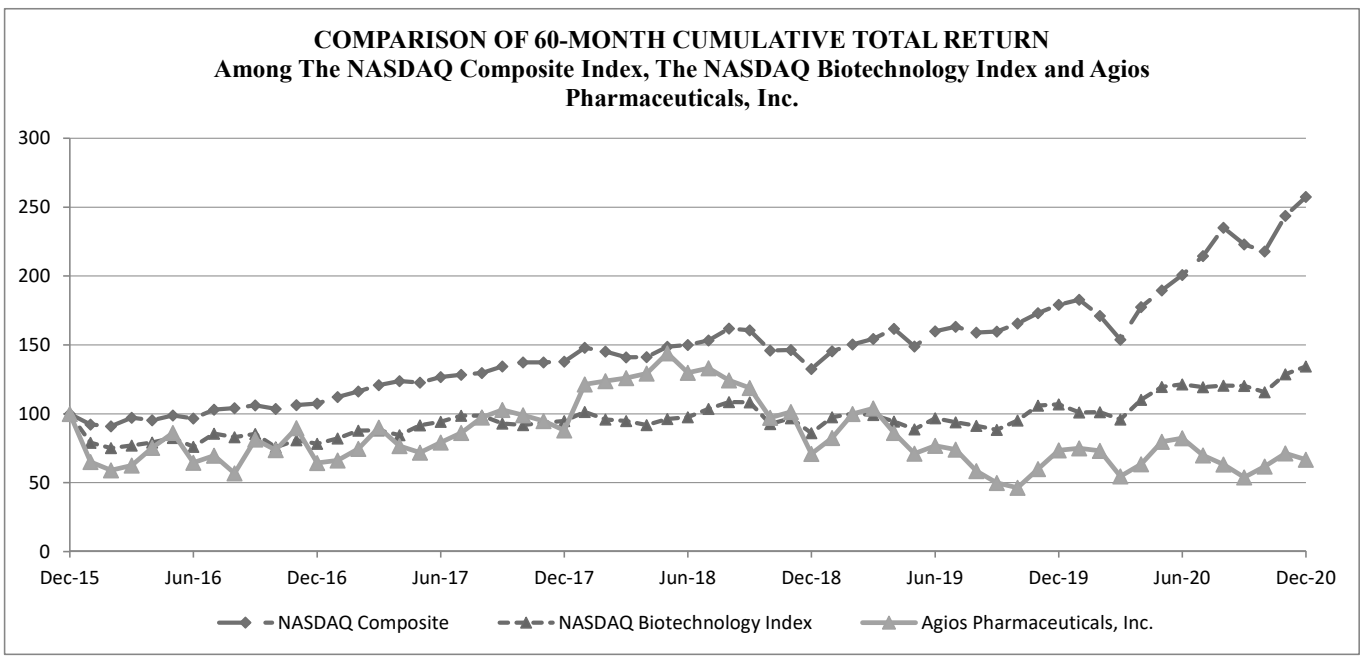
Securities Authorized for Issuance under Equity Compensation Plans

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, 2015 through December 31, 2020. The comparison assumes $100 was invested after the market closed on December 31, 2015 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 2020.

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)	2020	2019	2018 [1]	2017 [1]	2016 [1]
Results of Operations					
Total revenue	$ 203,196	$ 117,912	$ 94,387	$ 43,011	$ 69,892
Total cost and expenses [3]	519,345	544,245	456,866	363,805	270,877
Loss from operations	(316,149)	(426,333)	(362,479)	(320,794)	(200,985)
Net loss	$ (327,370)	$ (411,472)	$ (346,028)	$ (314,670)	$ (198,471)
Net loss per share – basic and diluted	$ (4.74)	$ (6.86)	$ (6.03)	$ (6.75)	$ (5.07)
Weighted-average number of common shares used in computing net loss per share – basic and diluted	68,997,879	59,994,539	57,418,300	46,587,631	39,126,400
Financial Position at Year End:					
Cash, cash equivalents and marketable securities	$ 670,537	$ 717,806	$ 805,421	$ 567,750	$ 573,564
Operating lease assets [2]	84,661	93,643	—	—	—
Total assets [2]	852,952	890,741	858,457	614,397	619,094
Deferred revenue	—	61,513	92,519	163,640	190,210
Operating lease liabilities [2]	104,551	112,716	—	—	—
Total liabilities [2]	453,452	250,213	170,920	238,894	260,503
Total stockholders' equity [2]	$ 399,500	$ 640,528	$ 687,537	$ 375,503	$ 358,591

(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 3. *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 3. *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 and $19,714 of cost reimbursement from related party for the years ended December 31, 2017 and 2016, 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 transforming 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 in the areas of genetically defined diseases, or GDDs, and, until the completion of the sale of our oncology business to Servier as described below, hematologic malignancies and solid tumors. To address our 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.

Proposed Sale of Oncology Business to Servier Pharmaceuticals, LLC (Servier)

On December 20, 2020, we entered into a Purchase and Sale Agreement, or the Purchase Agreement, with Servier. The Purchase Agreement provides for the sale of our commercial, clinical and research-stage oncology portfolio assets and pipeline, or oncology business, for a payment of $1.8 billion in cash at the closing, subject to certain adjustments for working capital of the oncology business at the closing and amounts for a representation and warranty insurance policy, and a payment of $200 million in cash, if, prior to January 1, 2027, vorasidenib is granted new drug application, or NDA, approval from the U.S. Food and Drug Administration, or FDA, with an approved label that permits vorasidenib's use as a single agent for the adjuvant treatment of patients with Grade 2 glioma that have an isocitrate dehydrogenase 1 or 2, or IDH1 or IDH2, mutation (and, to the extent required by such approval, the vorasidenib companion diagnostic test is granted an FDA premarket approval), as well as a royalty of 5% of U.S. net sales of TIBSOVO® from the close of the transaction through loss of exclusivity of TIBSOVO® and a royalty of 15% of U.S. net sales of vorasidenib from the first commercial sale of vorasidenib through loss of exclusivity of vorasidenib.

The transaction includes the proposed sale of our oncology business, including TIBSOVO®, our clinical-stage product candidates vorasidenib, AG-270 and AG-636, and our oncology research programs. Servier will also acquire our co-commercialization rights for Bristol Myers Squibb's IDHIFA®, the $25.0 million potential milestone payment, and conduct certain clinical development activities within the IDHIFA® development program.

The parties' obligations to consummate the proposed sale are subject to customary conditions, including the approval of the sale by the holders of at least a majority of our outstanding shares of common stock, the expiration or termination of the applicable waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, and the receipt of required regulatory approvals in Germany.

If the transaction closes, we will be a smaller, less diversified company with a more limited business concentrated on GDDs. As a result, we may be more susceptible to changing market conditions, including fluctuations and risks particular to the markets for patients with GDDs, than a more diversified company, which could adversely affect our business, financial condition and results of operations. In addition, the diversification of our revenues, costs and cash flows will diminish following the transaction, such that our results of operations, cash flows, working capital and financing requirements may be subject to increased volatility and our ability to fund capital expenditures and investments or satisfy other financial commitments may be diminished.

For more information on our proposed sale to Servier refer to "*Proposed Sale of Oncology Business to Servier Pharmaceuticals, LLC (Servier)"* within Item 1, *Business*.

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 a 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 October 2020, we announced the withdrawal of the MAA based on feedback from the EMA's Committee for Medicinal Products for Human Use (CHMP) that the available clinical data from our

single arm, uncontrolled Phase 1 trial did not sufficiently support a positive benefit-risk balance for the proposed indication. 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 were 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. On June 11, 2020 we sold our tiered, sales-based royalty rights on worldwide net sales of IDHIFA®, as well as our rights to receive up to $55.0 million in outstanding regulatory milestone payments from Bristol Myers Squibb, or BMS, to Royalty Pharma, or RPI, for $255.0 million. In addition, we and Celgene are currently evaluating enasidenib in the clinical trials described below.

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

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. We are currently evaluating vorasidenib in the clinical trials described below.

We are developing AG-270 for the treatment of cancers carrying a methylthioadenosine phosphorylase, or MTAP, deletion, which is present in approximately 15 percent of all cancers. AG-270 is an orally available selective potent inhibitor of methionine adenosyltransferase 2a, or MAT2A. On March 25, 2020, Celgene declined to exercise its right to opt into co-development and co-commercialization for AG-270, our MAT2A inhibitor development program, under our 2016 global research and collaboration agreement with Celgene, or the 2016 Agreement. We are currently evaluating AG-270 in a phase 1 dose-escalation and expansion trial in multiple tumor types carrying a MTAP, deletion, described below.

In the first quarter of 2020, we made the decision to cease the internal development of AG-636 for the treatment of hematologic malignancies, including lymphoma due to limited enrollment in our phase 1 trial in lymphoma. AG-636 is an inhibitor of the metabolic enzyme dihydroorotate dehydrogenase, or DHODH, licensed by us from Aurigene Discovery Technologies Limited, or Aurigene.

The lead product candidate in our genetically defined disease, or GDD, portfolio, mitapivat, is an activator of both wild-type and mutant pyruvate kinase-R, or PKR, 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. We are also developing AG-946, a next-generation PKR activator, for the potential treatment of hemolytic anemias and other indications.

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

Collaboration and License Agreements

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.

Celgene Corporation

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. On June 11, 2020, we sold our tiered, sales-based royalty rights on worldwide net sales of IDHIFA®, as well as our rights to receive up to $55.0 million in outstanding regulatory milestone payments from BMS, to RPI for $255.0 million. Under the 2010 Agreement, we remain eligible to receive a $25.0 million potential milestone payment for the enasidenib program upon achievement of a specified ex-U.S. commercial milestone event, as well as reimbursement for costs incurred for our co-commercialization efforts and development activities.

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. The initial four-year research term for the 2016 Agreement expired on May 17, 2020. On March 25, 2020 Celgene declined the option to extend the research agreement. Further, on April 10, 2020 Celgene notified us that they will be declining to elect any program as a continuation program under the 2016 agreement. Celgene had designated AG-270, our inhibitor MAT2A, as a development candidate under the 2016 Agreement. On March 25, 2020, Celgene notified us of their decision to decline their option to enter into a Development & Commercialization Agreement with respect to the MAT2A program under the 2016 Agreement.

Refer to Note 13. *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. On March 2, 2020, we amended the CStone Agreement to include Singapore as part of the CStone Territory. We retain development and commercialization rights for the rest of the world. Refer to Note 13. *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

Impact of COVID-19 on our Business

The spread of SARS-CoV-2 and the resulting disease COVID-19 has caused an economic downturn on a global scale, as well as significant volatility in the financial markets. In March 2020, the World Health Organization declared COVID-19 a pandemic. As of December 31, 2020, we have not experienced a significant financial or supply chain impact directly related to the pandemic but have experienced some disruptions to clinical operations, including timelines to complete patient enrollment in some of our clinical trials and delays in submission of regulatory filings, as further described below. In this time of uncertainty as a result of the COVID-19 pandemic, we are continuing to serve our customers while taking precautions to provide a safe work environment for our employees and customers. In March 2020, we established and implemented a work from home policy for our employees. In April 2020, we made internal resource allocation decisions in order to deliver on key business objectives and to increase our financial flexibility, including, pausing the development of certain preclinical research programs, delaying the start of certain longer-term clinical studies, limiting staff hiring, reducing the number of contract workers, and delaying or limiting information technology and facilities infrastructure projects. In June 2020, we implemented Phase 1 of our return to work program, which enabled all of our lab-based employees and related support personnel to return to our Cambridge office, and in September 2020 we began implementing Phase 2 of our return to work program by opening our Cambridge office to an additional, limited number of employees who prefer to work onsite. Our field-based employees engage with healthcare providers and other third parties remotely and, where local regulations allow, on a limited in-person basis. We are conducting our return to work program under strict guidelines as required by federal, state, and local authorities. We have been monitoring our supply chain network for disruptions due to the COVID-19 pandemic, and our third-party manufacturers remain largely unaffected, with any campaign delays experienced to date being limited to a few days in duration. Although global shipping continues to be disrupted due to the pandemic, we have not experienced a supply impact and have accrued additional safety stock of TIBSOVO® in order to further mitigate risk.

As the pandemic continues to unfold, the extent of the pandemic's effect on our operational and financial performance will depend in large part on future developments, which cannot be predicted with confidence at this time. Future developments include changes in the duration, scope and severity of the pandemic, the actions taken to contain or mitigate its impact, the impact on governmental programs and budgets, the development of treatments or vaccines, and the resumption of widespread economic activity. Any prolonged material disruption of our employees, suppliers, manufacturing, or customers could negatively impact our consolidated financial position, consolidated results of operations and consolidated cash flows. As a result, we may have to take further actions that we determine are in the best interests of our employees or as required by federal, state, or local authorities.

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, establishing a commercial infrastructure and marketing our approved products. To date, we have financed our operations primarily through commercial sales of TIBSOVO®, 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 $327.4 million, $411.5 million and $346.0 million for the years ended December 31, 2020, 2019 and 2018, respectively. As of December 31, 2020, we had an accumulated deficit of $1,843.5 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 expect that we will continue to incur significant expenses as we continue to advance and expand clinical development activities for our lead programs: ivosidenib, vorasidenib, mitapivat, AG-270, and AG-946; 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, 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 3, *Summary of Significant Accounting Polices* and Note 12, *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®. On June 11, 2020, we sold our tiered, sales-based royalty rights on worldwide net sales of IDHIFA®, as well as our rights to receive up to $55.0 million in outstanding regulatory milestone payments from Celgene, a wholly-owned subsidiary of BMS, to RPI for $255.0 million. Due to our continued involvement in the generation of these royalties through our co-promote right, we are treating the sale of these royalties as a liability and will continue to recognize royalty revenue 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, 2020, 2019 and 2018, respectively, were expensed prior to July 20, 2018 and, therefore, are not included in costs of sales during the years ended December 31, 2020, 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 to commercialize these product candidates. We are also unable to positively predict when future net cash inflows will commence from TIBSOVO®, vorasidenib, mitapivat, AG-270, AG-946 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 NDA enabling toxicology and clinical trials;
- 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, Singapore, and Taiwan to CStone, pursuant to an exclusive license agreement with CStone, or the CStone Agreement, discussed more fully above. We are required to 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, myelodysplastic syndromes, or MDS, cholangiocarcinoma and low grade glioma, where both the treatment options and prognosis for patients are poor.

The FDA has approved TIBSOVO® for the treatment of adult patients with R/R AML and a susceptible IDH1 mutation and for the treatment of 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. In December 2018, we submitted a MAA to the EMA for TIBSOVO® for the treatment of adult patients with IDH1 mutant-positive R/R AML. In October 2020, we withdrew the MAA based on feedback from the EMA's CHMP that the available clinical data from our single arm, uncontrolled Phase 1 trial did not sufficiently support a positive benefit-risk balance for the proposed indication. 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. Although we experienced disruptions related to the COVID-19 pandemic, we expect to complete enrollment in 2021.
- 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, although we experienced disruptions related to the COVID-19 pandemic.
- 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 reopened enrollment of its relapsed or refractory MDS arm and although we experienced disruptions related to the COVID-19 pandemic, we expect to complete enrollment in 2021.

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 trial has completed enrollment. The primary endpoint of the trial of progression-free survival was met and, although we experienced disruptions related to the COVID-19 pandemic, we expect to file an sNDA with the FDA for TIBSOVO® in cholangiocarcinoma in the first quarter of 2021.
- A phase 1 multi-center, open-label clinical trial of ivosidenib in patients with advanced IDH1 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.

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. The FDA has granted Celgene approval of IDHIFA® for the treatment of adult patients with R/R AML and an IDH2 mutation.

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. In August 2020, BMS announced that the trial did not meet the primary endpoint of overall survival in patients with IDH2 mutant positive AML.

Vorasidenib: brain penetrant pan-IDH program

Vorasidenib is an orally available, selective, brain-penetrant, pan-IDH mutant inhibitor. 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.
- The above mentioned 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, although we experienced disruptions related to the COVID-19 pandemic.

Mitapivat: PKR 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 a statistically significant and clinically meaningful reduction in transfusion burden in regularly-transfused patients with PK deficiency, and we have 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. Mitapivat has been granted orphan drug designation for the treatment of PK deficiency by the FDA and the EMA. Additionally, mitapivat has received orphan drug designation from the FDA for the treatment of thalassemia and sickle cell disease.

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 regularly-transfused patients with PK deficiency. The trial has completed enrollment. Although we experienced disruptions related to the COVID-19 pandemic, we reported in January 2021 that this trial met its primary endpoint of a statistically significant and clinically meaningful reduction in transfusion burden.
- ACTIVATE, a 1:1 randomized, placebo-controlled, global, pivotal trial of mitapivat in patients with PK deficiency who do not receive regular transfusions. The trial has completed enrollment. Although we experienced disruptions related to the COVID-19 pandemic, we reported in December 2020 that this trial met its primary endpoint of a statistically significant, sustained increase in hemoglobin compared to placebo. In addition, data from the trial demonstrated that treatment with mitapivat showed statistically significant improvement in key pre-specified secondary endpoints regarding patient reported outcomes.
- A phase 2, open-label safety and efficacy clinical trial of mitapivat in adult patients with non-transfusion-dependent α- and β-thalassemia. The trial has completed enrollment.
- In collaboration with the National Institutes of Health, or NIH, we are evaluating mitapivat in a phase 1 trial in patients with sickle cell disease pursuant to a cooperative research and development agreement. The trial is ongoing and enrolling patients, although the NIH experienced disruptions related to the COVID-19 pandemic.

We plan to submit an NDA for mitapivat in adults with PK deficiency to the FDA in the second quarter of 2021, and plan to submit an MAA for mitapivat in adults with PK deficiency to the EMA in mid-2021, with a potential 2022 commercial launch in both geographies. We will continue to grow our US commercial infrastructure and evaluate all options for the commercialization and continued development of mitapivat outside of the United States in order to maximize the benefit to patients and value to our shareholders, including through exploring potential partnership opportunities.

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 cancers. 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. On April 10, 2020 Celgene notified us that they declined to elect any program as a continuation program under the 2016 agreement. With this decision we are no longer eligible for up to $168.8 million in clinical and regulatory milestone payments under the 2016 Agreement.

We are evaluating AG-270 in a phase 1 trial in multiple tumor types carrying an MTAP deletion. The first part of the trial, was a dose-escalation of AG-270 and is complete. The next part of the trial consists of two arms evaluating AG-270 in combination with taxanes. One arm of the trial 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 are enrolling patients, although we experienced disruptions related to the COVID-19 pandemic.

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 were evaluating AG-636, an inhibitor of DHODH, licensed to us from Aurigene in a phase 1 dose-escalation trial in subjects with advanced lymphomas. In the first quarter of 2020, we made the decision to halt internal development of AG-636, due to limited enrollment in this trial, and will continue to wind down the trial until the close of the proposed sale to Servier.

AG-946: Next-generation PKR Activator

- We are developing AG-946, a next-generation PKR activator, for the potential treatment of hemolytic anemias. We are evaluating AG-964, in a phase 1 trial of AG-946 in healthy volunteers and in patients with SCD. The trial is currently enrolling healthy volunteers, although we experienced disruptions related to the COVID-19 pandemic.

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 in fully understanding and evaluating our financial condition and results of operations.

Revenue Recognition

Under Accounting Standards Codification 606, *Revenue from Contracts with Customers*, or 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 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, 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. In addition, we receive sales order management, data and distribution services from certain Customers.

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 include 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 and 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, or SSPs, 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 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 CRO 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.

Liability related to sale of future revenue

We treat the sale of future revenue to RPI as a debt financing, as we have significant continuing involvement in the generation of the cash flows. As result, we recorded the proceeds from this transaction as a liability related to the sale of future revenue to be amortized to interest expense using the effective interest rate method over the life of the arrangement.

The liability related to sale of future revenue and the related interest expense are based on our current estimates of future royalties expected to be paid over the life of the arrangement. We will periodically assess the expected royalty payments using forecasts from external sources. To the extent our future estimates of royalty payments are greater or less than previous estimates or the estimated timing of such payments is materially different than its previous estimates, we will prospectively recognize related non-cash interest expense.

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, 2020, 2019 and 2018

Total Revenue

(In thousands)	2020	2019	2018
Revenues:			
Product revenue, net	$ 121,089	$ 59,851	$ 13,841
Collaboration revenue – related party	68,274	39,257	60,661
Collaboration revenue – other	3,571	8,262	12,670
Royalty revenue – related party	10,262	10,542	7,215
Total revenue	$ 203,196	$ 117,912	$ 94,387

Total Revenue – 2020 vs 2019 – The increase in total revenue of $85.3 million in 2020 compared to 2019 was primarily due to an increase in product revenue of $61.2 million and an increase in collaboration revenue - related party of $29.0 million. The increase in product revenue was primarily the result of increased sales volume of TIBSOVO®. The increase in collaboration revenue-related party was primarily due to our updated estimate of the future costs of research and development services to complete one of our performance obligations under the 2016 Agreement which had been recognized over time.

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 with the EMA for IDHIFA® for IDH2 mutant-positive R/R AML in 2018.

We generate product revenue from sales of TIBSOVO® to Customers. If the proposed sale to Servier of our oncology business is completed, we will no longer sell TIBSOVO® and our product revenue will significantly decrease until such time as we commercialize another product candidate.

Under the 2010 Agreement with Celgene, we are reimbursed for costs incurred for our co-commercialization efforts and development activities. If the proposed sale to Servier of our oncology business is completed, Servier will acquire our co-commercialization right and responsibilities for BMS's IDHIFA®, and our collaboration revenue – related party will significantly decrease. Further, the $25.0 million milestone remaining under the 2010 Agreement after the sale of our IDHIFA® royalty revenue to RPI, will be payable to Servier following the close of the proposed sale.

As partial consideration for our proposed sale to Servier, we are entitled to a royalty of 5% of U.S. net sales of TIBSOVO® from the closing through the loss of exclusivity of TIBSOVO® and a royalty of 15% of U.S. net sales of vorasidenib from the first commercial sale of vorasidenib through loss of exclusivity of vorasidenib. However, we cannot predict what success, if any, Servier may have in the United States with respect to sales of TIBSOVO® and vorasidenib and, therefore, the amount of royalty payments that we can expect to receive from Servier under the terms of the Purchase Agreement prior to the loss of exclusivity of these products.

Total Operating Expenses

(In thousands)	2020	2019	2018
Cost and expenses:			
Cost of sales	$ 2,805	$ 1,317	$ 1,397
Research and development	367,470	410,894	341,324
Selling, general and administrative	149,070	132,034	114,145
Total Operating Expenses	$ 519,345	$ 544,245	$ 456,866

Total Operating Expenses – 2020 vs 2019 – The decrease in total operating expenses of $24.9 million in 2020 compared to 2019 was primarily due to a decrease of $43.4 million in research and development expenses, which is described below under Research and Development Expenses, partially offset by an increase of $17.0 million in selling, general and administrative expense due to higher personnel costs, including stock-based compensation expense, related to additional hiring for our workforce. Included in selling, general and administrative expense is approximately $5.0 million in professional fees related to entering into the proposed sale transaction with Servier. In addition, our cost of sales increased moderately in 2020 as we continue to deplete our finished goods inventory that was expensed prior to receiving FDA approval of TIBSOVO®.

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.

Cost of sales consists primarily of manufacturing costs for sales of TIBSOVO®. If our proposed sale of our oncology business to Servier is completed, our cost of sales will significantly decrease until such time as we commercialize another product candidate.

Research and Development Expenses

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

(In thousands)	2020	2019	2018
IDH1 inhibitor (ivosidenib)	$ 51,907	$ 79,087	$ 74,600
IDH2 inhibitor (enasidenib)	1,163	3,983	4,140
Pan IDH inhibitor (vorasidenib (AG-881))	18,322	23,060	7,005
PKR activator (mitapivat)	48,669	47,481	31,254
MAT2A inhibitor (AG-270)	6,500	11,058	9,656
DHODH inhibitor (AG-636) discontinued	2,987	8,663	4,428
Next-Gen PKR activator (AG-946)	8,378	5,849	6,314
Other research and platform programs	32,979	38,208	30,193
Total direct research and development expenses	170,905	217,389	167,590
Compensation and related expenses	146,515	144,888	135,227
Facilities and IT related expenses & other	50,050	48,617	38,507
Total indirect research and development expenses	196,565	193,505	173,734
Total research and development expense	$ 367,470	$ 410,894	$ 341,324

Total Research and Development Expenses – 2020 vs 2019 – The decrease in research and development expenses of $43.4 million in 2020 compared to 2019 was primarily due to a $46.5 million decrease in our direct expenses. The decrease in direct expenses was primarily due to a $27.2 million decrease in ivosidenib costs, a $5.7 million decrease in AG-636 costs, and a $5.2 million decrease in other research and platform programs. The decrease in ivosidenib costs was primarily due to decreased trial activities for the ClarIDHy trial and decreased clinical costs driven by $6.5 million in milestones achieved by HOVON during the year ended December 31, 2019 for the initiation of the HO150/AMLSG29 trial. The decrease in AG-636 costs was primarily due to the decision to halt internal development of AG-636 in the first quarter of 2020 due to limited trial enrollment, and a $2.0 million milestone payment due to Aurigene upon first patient dosing within the phase 1 lymphoma trial in the second quarter of 2019. The decrease in other research and platform programs was primarily driven by planned decreased activity on various exploratory and discovery activities and a $4.0 million upfront payment for exploratory efforts in the second quarter of 2019.

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.

If our proposed sale to Servier is completed, we will no longer operate the oncology business. We will be a smaller, less diversified company with a more limited business concentrated on GDDs. As a result, our direct research and development expenses for ivosidenib, enasidenib, vorasidenib, AG-270 and AG-636 will cease, and our direct research and development expenses will largely be concentrated on mitapivat and AG-946.

Interest Income and Expense

(In thousands)	2020	2019	2018
Interest income, net	$ 6,611	$ 14,861	$ 16,451
Non-cash interest expense for the sale of future revenue	(17,832)	—	—

Interest Income and Non-Cash Interest Expense for the Sale of Future Revenue – 2020 vs 2019 – The decrease in interest income, net in 2020 compared to 2019 is primarily attributable to the decrease in interest rates at the end of the first quarter of 2020, which reduced the interest rates earned by 0.50% to 1.50% from prior periods and the decrease in our outstanding marketable securities balance for the year ended December 31, 2020. The non-cash interest expense for the sale of future

revenue in 2020 was due to the interest expense associated with the sale of future revenue to RPI recorded in the year ended December 31, 2020.

Interest Income and Expense – 2019 vs 2018 – The decrease in interest income, net 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.

Loss from Operations and Net Loss

(In thousands)	2020	2019	2018
Loss from operations	$(316,149)	$(426,333)	$ (362,479)
Net loss	(327,370)	(411,472)	(346,028)

Loss from Operations and Net Loss – 2020 vs 2019 – The decrease in loss from operations and net loss in 2020 compared to 2019 is primarily driven by higher total revenue as described above in Total Revenue and lower operating expenses as described above in Total Operating Expenses.

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.

Liquidity and Capital Resources

Sources of liquidity

Since our inception, and through December 31, 2020, we have funded our operations through upfront, milestone, extension, cost reimbursement and royalty payments related to our collaboration agreements, product sales, proceeds from the rale of our royalty rights, 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.

On June 11, 2020, we sold our tiered, sales-based royalty rights on worldwide net sales of IDHIFA® (enasidenib), as well as our rights to receive up to $55.0 million in outstanding regulatory milestone payments from BMS, to RPI for $255.0 million. Under the 2010 Agreement, we remain eligible to receive a $25.0 million potential milestone payment for the enasidenib program. The potential milestone payment is a $25.0 million milestone payment upon achievement of a specified ex-U.S. commercial milestone event, as well as reimbursement for costs incurred for our co-commercialization efforts and development activities.

On April 30, 2020, we entered into an at-the-market sales agreement, or the 2020 sales agreement, with Cowen & Company LLC, or Cowen, pursuant to which we may offer and sell shares of our common stock having an aggregate offering price of up to $250.0 million through Cowen pursuant to a universal shelf registration statement on Form S-3 filed with the SEC on April 30, 2020. As of December 31, 2020, $250.0 million in common stock remained available for future issuance under the 2020 sales agreement.

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 addition to our existing cash, cash equivalents and marketable securities, we are eligible to earn milestone payments, cost reimbursements, and royalty payments under our collaboration agreements with Celgene and CStone. 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.

In December 2020, we entered into the Purchase Agreement with Servier. The base purchase price of $1.8 billion is subject to a working capital adjustment and will increase or decrease based on the amount of working capital of the oncology business as of the completion of the transaction relative to a specified working capital target. It is not possible to determine with precision the amount of working capital the oncology business may have as of the completion of the transaction. It is possible that the working capital adjustment may result in a meaningful reduction to the purchase price. Whether the regulatory approval milestone for vorasidenib will be achieved is also subject to various risks and uncertainties. The transaction includes the sale of

TIBSOVO®, a current source of our revenue, and vorasidenib. We cannot predict what success, if any, Servier may have in the United States with respect to sales of TIBSOVO® and vorasidenib and, therefore, the amount of royalty payments that we can expect to receive from Servier under the terms of the Purchase Agreement prior to the loss of exclusivity of these products.

The parties' obligations to consummate the proposed sale are subject to customary conditions, including the approval of the sale by the holders of at least a majority of our outstanding shares of common stock, the expiration or termination of the applicable waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, and the receipt of required regulatory approvals in Germany.

Our board of directors may cause us to terminate the Purchase Agreement in order to enter into a definitive agreement relating to a superior proposal, subject to complying with certain conditions set forth in the Purchase Agreement. If we terminate the Purchase Agreement in order to enter into definitive agreements with respect to a superior proposal, we may be required to pay to Servier a termination fee of $45 million prior to or concurrently with such termination.

Cash flows

The following table provides information regarding our cash flows for the years ended December 31, 2020, 2019 and 2018:

(In thousands)	2020	2019	2018
Net cash used in operating activities	$ (290,759)	$ (370,622)	$ (304,421)
Net cash provided by (used in) investing activities	75,746	91,440	(273,825)
Net cash provided by financing activities	261,518	289,611	546,024
Net change in cash and cash equivalents	$ 46,505	$ 10,429	$ (32,222)

Net cash used in operating activities

During the year ended December 31, 2020, we received $123.8 million from sales of TIBSOVO®, $7.9 million in royalty payments and $6.1 million in cost reimbursements related to our Collaboration Agreements with Celgene, $7.0 million in interest received, and $3.6 million in cost reimbursements related to our CStone Agreement. These amounts were offset by operating expenses driven by research and development costs described above in Research and Development Expenses and increased staffing needs due to our expanding operations. Net cash used in operating activities does not include the $5.0 million in professional fees related to entering into the proposed sale transaction with Servier in the fourth quarter of 2020.

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.

Net cash provided by (used in) investing activities

The cash provided by investing activities for the year ended December 31, 2020 was primarily the result of lower purchases of marketable securities than proceeds from maturities and sales of marketable securities, offset by $14.9 million in purchases of property and equipment.

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.

Net cash provided by financing activities

The cash provided by financing activities for the year ended December 31, 2020 was primarily the result of net proceeds of $250.5 million from the sale of our tiered, sales-based royalty rights on worldwide net sales of IDHIFA® (enasidenib) and our

ex-US regulatory milestones to RPI in June 2020, and the $11.3 million of proceeds 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, 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.

Funding requirements

Until the completion of the proposed sale of our oncology business to Servier, 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, 2020, together with anticipated product revenue, anticipated interest income and anticipated expense reimbursements under our collaboration and license agreements, but excluding any additional program-specific milestone payments or any proceeds from the proposed sale of our oncology business to Servier, if such sale is consummated, will enable us to fund our operating expenses and capital expenditure requirements to the end of 2022. Following the completion of the transaction with Servier and any subsequent shareholder returns, we expect to have sufficient capital to fund operations through major catalysts and to cash-flow positivity without the need to raise additional equity. Our future capital requirements will depend on many factors, including:

- the timing and likelihood of the closing of the sale of our oncology business to Servier and the amount of consideration we may receive in connection with the sale;
- 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 related to approved medicines;
- levels of product revenue from sales of approved medicines;
- the costs associated with preparation for the potential commercial launch of one or more of our product candidates;
- our ability to establish and maintain additional collaborations on favorable terms, if at all;
- our ability to successfully execute on our strategic plans;
- operational delays due to the ongoing COVID-19 pandemic; and
- the extent to which we acquire or in-license, or monitor or out-license, other medicines and technologies.

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, licensing arrangements and other nondilutive strategic transactions. We do not have any committed potential external source of funds other than our collaborations, and the proposed sale of our oncology business to Servier. 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, 2020:

	Payments due by period				
(In thousands)	Total	Less than 1 year	1-3 years	3-5 years	More than 5 years
Operating lease obligations	$ 130,649	$ 13,198	$ 34,899	$ 38,167	$ 44,385
Manufacturing arrangements	4,743	1,205	3,538	—	—

We enter into agreements in the normal course of business with CROs for clinical trials and contract manufacturing organizations, or 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 did not make any payments during the year ended December 31, 2020 and 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, 2020 and, if satisfied, the timing of payment for these amounts was not reasonably estimable at December 31, 2020. 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.

Lastly, in connection with the proposed sale of our oncology business to Servier, if the agreement is terminated under specified conditions, we would be required to make a one-time payment of $45 million to Servier.

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, 2020, we had cash, cash equivalents and marketable securities of $670.5 million, consisting primarily of investments in U.S. Treasuries, 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, 2020 and December 31, 2019, 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, 2020, 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, 2020. 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, 2020, 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, 2020, 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, 2020 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 2021 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 2021 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 2021 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 2021 Annual Meeting of Stockholders and is incorporated herein by reference.

Item 14. Principal Accountant 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 2021 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-39 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
2.1+	Purchase and Sale Agreement, dated as of December 20, 2020, by and among the Registrant, Servier Pharmaceuticals, LLC, and, solely for purposes of guaranteeing certain obligations of the Purchaser, Servier S.A.S	8-K	001-36014	December 22, 2020	2.1	
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	Description of Securities Registered Under Section 12 of the Securities Exchange Act of 1934	10-K	001-36014	February 19, 2020	4.3	
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	

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
10.8	Form of Indemnification Agreement between the Registrant and each of its Executive Officers and Directors	S-1	333-189216	July 11, 2013	10.12	
10.9#	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	
10.10†	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	
10.11†	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	
10.12	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	
10.13	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	
10.14	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	
10.15#	Summary Description of Annual Cash Incentive Program	10-Q	001-36014	May 11, 2015	10.1	
10.16	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	
10.17†	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	
10.18†	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	
10.19#	Form of Performance Share Unit Agreement under 2013 Stock Incentive Plan	10-K	001-36014	February 26, 2016	10.25	
10.20#	Severance Benefits Plan	8-K	001-36014	April 22, 2016	10.1	
10.21†	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	
10.22#	Letter Agreement between the Registrant and Andrew Hirsch, effective August 11, 2016	8-K	001-36014	August 16, 2016	99.2	
10.23	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	
10.24	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	
10.25	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	
10.26#	Form of Restricted Stock Unit Agreement under 2013 Stock Incentive Plan (for employees)	10-Q	001-36014	May 4, 2018	10.1	
10.27†	License Agreement, dated June 25, 2018, by and between Agios Pharmaceuticals, Inc. and CStone Pharmaceuticals	10-Q	001-36014	August 2, 2018	10.2	
10.28#	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	
10.29#	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	
10.30#	Form of Restricted Stock Unit Agreement under 2013 Stock Incentive Plan (for directors)	10-K	001-36014	February 14, 2019	10.32	
10.31	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	
10.32	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	
10.33	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	
10.34#	Letter Agreement, dated as of September 17, 2019, between the Registrant and Jonathan Biller	10-K	001-36014	February 19, 2020	10.35	
10.35#	Letter Agreement, dated as of October 7, between the Registrant and Bruce Car	10-Q	001-36014	April 30, 2020	10.1	
10.36†	Amendment to Master Research and Collaboration Agreement, dated as of February 5, 2020, by and among the Registrant, Celgene Corporation and Celgene RIVOT Ltd	10-Q	001-36014	April 30, 2020	10.2	
10.37†	Amendment I to License Agreement, dated as of March 2, 2020, by and between the Registrant and CStone Pharmaceuticals	10-Q	001-36014	April 30, 2020	10.3	
10.38†	Amendment II to License Agreement, dated as of March 2, 2020, by and between the Registrant and CStone Pharmaceuticals	10-Q	001-36014	April 30, 2020	10.4	
10.39	Sales Agreement, dated April 30, 2020, by and between the Registrant and Cowen and Company, LLC	S- 3ASR	333-237930	April 30, 2020	1.2	

Exhibit Number	Description of Exhibit	Incorporated by Reference				Filed Herewith
		Form	File Number	Date of Filing	Exhibit Number	
10.40†	Royalty Purchase Agreement, dated as of June 11, 2020, by and between the Registrant and RPI 2019 Intermediate Finance Trust	10-Q	001-36014	July 30, 2020	10.2	
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
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					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.
+	Pursuant to Item 601(6)(2) of Regulation S-K, the disclosure schedules to the Purchase Agreement (identified therein) have been omitted from this Current Report on Form 8-K and will be furnished to the SEC supplementally upon request.
*	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 25, 2021

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 25, 2021
/s/ Jonathan Biller Jonathan Biller	Chief Financial Officer and Head of Legal and Corporate Affairs (Principal financial officer)	February 25, 2021
/s/ Carman Alenson Carman Alenson	Vice President of Accounting, Treasury and Tax (Principal accounting officer)	February 25, 2021
/s/ Paul J. Clancy Paul J. Clancy	Director	February 25, 2021
/s/ Ian Clark Ian Clark	Director	February 25, 2021
/s/ Kaye Foster Kaye Foster	Director	February 25, 2021
/s/ Maykin Ho Maykin Ho, Ph.D.	Director	February 25, 2021
/s/ John M. Maraganore John M. Maraganore, Ph.D.	Director	February 25, 2021
/s/ David Scadden David Scadden, M.D.	Director	February 25, 2021
/s/ David P. Schenkein David P. Schenkein, M.D.	Director	February 25, 2021

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, 2020 and 2019, 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, 2020, 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, 2020, 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, 2020 and 2019, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2020 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, 2020, based on criteria established in *Internal Control - Integrated Framework* (2013) issued by the COSO.

Changes in Accounting Principles

As discussed in Note 3 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.

Liability related to sale of future revenue

As described in Notes 3 and 10 to the consolidated financial statements, on June 11, 2020 the Company sold its tiered, sales-based royalty rights on worldwide net sales of IDHIFA®, as well as rights to receive up to $55 million in regulatory milestone payments from Bristol Myers Squibb to Royalty Pharma ("RPI") for $255 million. Management accounted for the sale of future revenue to RPI as a debt financing, as the Company continues to have significant continuing involvement in the generation of the cash flows. Management applied significant judgment in determining the appropriate accounting treatment for the transaction. The liability related to sale of future revenue and the related interest expense are based on Management's current estimates of future royalties expected to be paid over the life of the arrangement. Management periodically assesses the expected royalty payments using forecasts from external sources. The Company recognized non-cash interest expense for the sale of future revenue of $17.8 million for the year ended December 31, 2020, and the liability related to the sale of future revenue was $261.3 million as of December 31, 2020.

The principal considerations for our determination that performing procedures relating to the liability related to the sale of future revenue is a critical audit matter are the significant judgment by management in determining the appropriate accounting for the transaction and the valuation of the liability related to sale of future revenue. This in turn led to a high degree of auditor judgment, effort, and subjectivity in performing procedures and evaluating management's determination of the accounting for the transaction and the assumption related to the current estimates of future royalties expected to be paid over the life of the arrangement.

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 management's determination of the accounting treatment for the transaction, as well as controls over the development of the assumption related to the current estimates of future royalties expected to be paid over the life of the arrangement. These procedures also included, among others, evaluating whether the transaction has been properly accounted for in accordance with the relevant accounting standards, testing management's process for determining the valuation of the liability related to the sale of future revenue, testing the completeness and accuracy of underlying data used in determining the valuation of the liability, and evaluating the significant assumption used by management related to the current estimate of future royalties expected to be paid over the life of the arrangement. Evaluating management's assumption related to the current estimate of future royalties expected to be paid over the life of the arrangement involved evaluating whether the assumption used by management was reasonable considering the terms of the agreement, consistency with external market and industry data, and consistency with evidence obtained in other areas of the audit.

/s/ PricewaterhouseCoopers LLP

Boston, Massachusetts
February 25, 2021

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

Agios Pharmaceuticals, Inc.

Consolidated Balance Sheets

(In thousands) December 31:	2020	2019
Assets		
Current assets:		
Cash and cash equivalents	$ 127,436	$ 80,931
Marketable securities	445,493	483,946
Accounts receivable, net	21,328	8,952
Collaboration receivable – related party	2,123	1,539
Collaboration receivable – other	1,948	1,928
Royalty receivable – related party	—	2,900
Inventory	14,698	7,331
Prepaid expenses and other current assets	23,651	24,177
Total current assets	636,677	611,704
Marketable securities	97,608	152,929
Operating lease assets	84,661	93,643
Property and equipment, net	32,291	31,472
Financing lease assets	590	993
Other non-current assets	1,125	—
Total assets	$ 852,952	$ 890,741
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 26,844	$ 21,896
Accrued expenses	60,140	53,142
Deferred revenue – related party	—	10,933
Operating lease liabilities	7,093	6,642
Financing lease liabilities	317	273
Total current liabilities	94,394	92,886
Deferred revenue, net of current portion – related party	—	50,580
Operating lease liabilities, net of current portion	97,458	106,074
Financing lease liabilities, net of current portion	331	673
Liability related to the sale of future revenue, net of debt issuance costs	261,269	—
Total liabilities	453,452	250,213
Commitments and contingent liabilities (Note 11)		
Stockholders' equity:		
Preferred stock, $0.001 par value; 25,000,000 shares authorized, no shares issued and outstanding at December 31, 2020 and 2019	—	—
Common stock, $0.001 par value; 125,000,000 shares authorized and 69,293,920 and 68,401,105 shares issued and outstanding at December 31, 2020 and 2019, respectively	69	68
Additional paid-in capital	2,242,801	2,156,363
Accumulated other comprehensive income	105	202
Accumulated deficit	(1,843,475)	(1,516,105)
Total stockholders' equity	399,500	640,528
Total liabilities and stockholders' equity	$ 852,952	$ 890,741

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:	2020	2019	2018
Revenues:			
Product revenue, net	$ 121,089	$ 59,851	$ 13,841
Collaboration revenue – related party	68,274	39,257	60,661
Collaboration revenue – other	3,571	8,262	12,670
Royalty revenue – related party	10,262	10,542	7,215
Total revenue	203,196	117,912	94,387
Cost and expenses:			
Cost of sales	2,805	1,317	1,397
Research and development	367,470	410,894	341,324
Selling, general and administrative	149,070	132,034	114,145
Total cost and expenses	519,345	544,245	456,866
Loss from operations	(316,149)	(426,333)	(362,479)
Interest income, net	6,611	14,861	16,451
Non-cash interest expense for the sale of future revenue	(17,832)	—	—
Net loss	$ (327,370)	$ (411,472)	$ (346,028)
Net loss per share – basic and diluted	$ (4.74)	$ (6.86)	$ (6.03)
Weighted-average number of common shares used in computing net loss per share – basic and diluted	68,997,879	59,994,539	57,418,300

See accompanying Notes to Consolidated Financial Statements.

Agios Pharmaceuticals, Inc.

Consolidated Statements of Comprehensive Loss

(In thousands) Years Ended December 31:	2020	2019	2018
Net loss	$ (327,370)	$ (411,472)	$ (346,028)
Other comprehensive (loss) income:			
Unrealized (loss) gain on available-for-sale securities	(97)	2,373	(782)
Comprehensive loss	$ (327,467)	$ (409,099)	$ (346,810)

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, 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
Unrealized loss on available-for-sale securities	—	—	—	(97)	—	(97)
Net loss	—	—	—	—	(327,370)	(327,370)
Stock-based compensation expense	—	—	75,122	—	—	75,122
Issuance of common stock under stock incentive and employee stock purchase plans	892,815	1	11,316	—	—	11,317
Issuance of common stock for follow-on offering	—	—	—	—	—	—
Other	—	—	—	—	—	—
Balance at December 31, 2020	69,293,920	$ 69	$ 2,242,801	$ 105	$ (1,843,475)	$ 399,500

See accompanying Notes to Consolidated Financial Statements.

Agios Pharmaceuticals, Inc.

Consolidated Statements of Cash Flows

(In thousands) Years Ended December 31:	2020	2019	2018
Operating activities			
Net loss	$ (327,370)	$ (411,472)	$ (346,028)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	9,984	8,087	7,172
Stock-based compensation expense	75,122	72,373	73,357
Net amortization of premium (accretion of discount) on marketable securities	3,022	(3,195)	(3,837)
Loss on disposal of property and equipment	—	1,052	20
Non-cash operating lease expense	8,982	8,532	—
Non-cash interest expense associated with the sale of future revenue	17,832	—	—
Non-cash royalty revenue	(7,294)	—	—
Changes in operating assets and liabilities:			
Accounts receivable, net	(12,376)	(3,876)	(5,076)
Collaboration receivable – related party	(584)	923	(14)
Collaboration receivable – other	(20)	(1,258)	(670)
Royalty receivable – related party	2,900	(666)	(1,012)
Inventory	(7,367)	(6,462)	(869)
Prepaid expenses and other current and non-current assets	(599)	(7,742)	1,148
Accounts payable	5,889	3,716	(5,488)
Accrued expenses	10,760	7,233	8,623
Deferred revenue – related party	(61,513)	(31,006)	(31,665)
Operating lease liabilities	(8,127)	(6,861)	—
Deferred rent	—	—	(82)
Net cash used in operating activities	(290,759)	(370,622)	(304,421)
Investing activities			
Purchases of marketable securities	(557,030)	(488,566)	(933,320)
Proceeds from maturities and sales of marketable securities	647,685	592,177	666,481
Purchases of property and equipment	(14,909)	(12,171)	(6,986)
Net cash provided by (used in) investing activities	75,746	91,440	(273,825)
Financing activities			
Payments on financing lease obligations	(336)	(113)	—
Proceeds from public offering of common stock, net of reimbursements	—	277,201	516,206
Reimbursement (payment) of public offering costs	—	—	(391)
Proceeds from the sale of future revenue, net of issuance costs	250,537	—	—
Net proceeds from stock option exercises and employee stock purchase plan	11,317	12,523	30,209
Net cash provided by financing activities	261,518	289,611	546,024
Net change in cash and cash equivalents	46,505	10,429	(32,222)
Cash and cash equivalents at beginning of the period	80,931	70,502	102,724
Cash and cash equivalents at end of the period	$ 127,436	$ 80,931	$ 70,502
Supplemental disclosure of non-cash investing and financing transactions:			
Additions to property and equipment in accounts payable and accrued expenses	$ 465	$ 5,168	$ 1,106
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, "the Company," "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 transforming 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 in the areas of genetically defined diseases, or GDDs, and, until the completion of the sale of our oncology business to Servier as described below, hematologic malignancies and solid tumors. To address our 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 a 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 October 2020, we announced the withdrawal of the MAA based on feedback from the EMA's Committee for Medicinal Products for Human Use (CHMP) that the available clinical data from our single arm, uncontrolled Phase 1 trial did not sufficiently support a positive benefit-risk balance for the proposed indication.

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 were 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. On June 11, 2020 we sold our tiered, sales-based royalty rights on worldwide net sales of IDHIFA®, as well as our rights to receive up to $55.0 million in outstanding regulatory milestone payments from Bristol Myers Squibb, or BMS, to Royalty Pharma, or RPI, for $255.0 million.

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

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. In the first quarter of 2020, we made the decision to halt internal development of AG-636, due to limited enrollment in this trial, and will continue to wind down the trial during 2021.We are currently evaluating AG-636 in the phase 1 dose-escalation trial in lymphoma.

The lead product candidate in our GDD 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. We are also developing AG-946, a next-generation PKR activator, for the potential treatment of hemolytic anemias and other indications.

In addition to the aforementioned development programs, we are seeking to advance a number of early-stage discovery programs in our focus areas of GDDs, malignant hematology and solid tumors 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

On June 11, 2020, we sold our tiered, sales-based royalty rights on worldwide net sales of IDHIFA® (enasidenib), as well as our rights to receive up to $55.0 million in outstanding regulatory milestone payments from BMS, to RPI for $255.0 million. Under the 2010 Agreement, we remain eligible to receive a $25.0 million potential milestone payment for the enasidenib program. The potential payment is a $25.0 million milestone payment upon achievement of a specified ex-U.S. commercial milestone event, as well as reimbursement for costs incurred for our co-commercialization efforts and development activities.

On April 30, 2020, we entered into an at-the-market sales agreement, or the 2020 sales agreement, with Cowen & Company LLC, or Cowen, pursuant to which we may offer and sell shares of our common stock having an aggregate offering price of up to $250.0 million through Cowen pursuant to a universal shelf registration statement on Form S-3 filed with the SEC on April 30, 2020. As of December 31, 2020, $250.0 million in common stock remained available for future issuance under the 2020 sales agreement.

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, 2020, we had cash, cash equivalents and marketable securities of $670.5 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. Proposed Sale of Oncology Business to Servier Pharmaceuticals, LLC (Servier)

On December 20, 2020, we entered into a Purchase and Sale Agreement, or the Purchase Agreement, with Servier. The Purchase Agreement provides for the sale of our commercial, clinical and research-stage oncology portfolio assets and pipeline, or oncology business, for a payment of $1.8 billion in cash at the closing, subject to certain adjustments for working capital of the oncology business at the closing and amounts for a representation and warranty insurance policy, and a payment of $200 million in cash, if, prior to January 1, 2027, vorasidenib is granted new drug application, or NDA, approval from the U.S. Food and Drug Administration, or FDA, with an approved label that permits vorasidenib's use as a single agent for the adjuvant treatment of patients with Grade 2 glioma that have an isocitrate dehydrogenase 1 or 2, or IDH1 or IDH2, mutation (and, to the extent required by such approval, the vorasidenib companion diagnostic test is granted an FDA premarket approval), as well as a royalty of 5% of U.S. net sales of TIBSOVO® from the close of the transaction through loss of exclusivity of TIBSOVO® and a royalty of 15% of U.S. net sales of vorasidenib from the first commercial sale of vorasidenib through loss of exclusivity of vorasidenib.

The transaction includes the proposed sale of our oncology business, including TIBSOVO®, our clinical-stage product candidates vorasidenib, AG-270 and AG-636, and our oncology research programs. Servier will also acquire our co-commercialization rights for Bristol Myers Squibb's IDHIFA®, the $25.0 million potential milestone payment, and conduct certain clinical development activities within the IDHIFA® development program.

The proposed sale has been approved by our Board of Directors. The parties' obligations to consummate the proposed sale are subject to customary conditions, including the approval of the sale by the holders of at least a majority of our outstanding shares of common stock, the expiration or termination of the applicable waiting period under the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended, and the receipt of required regulatory approvals in Germany.

Subject to certain exceptions, we and Servier have agreed to use reasonable best efforts to cause the sale to be completed. The Purchase Agreement includes certain termination provisions for both Servier and us and provides that, in connection with a

termination of the Purchase Agreement under specified circumstances, we may be required to pay Servier a termination fee of $45 million.

We currently expect to complete the transaction at the end of the first quarter of or in the beginning of the second quarter of 2021.

Note 3. 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., Agios Italy S.R.L., Agios France SARL, 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. On an ongoing basis we evaluate our estimates, judgments and methodologies. We base our estimates on historical experience and on various other assumptions that we believe are reasonable, the results of which form the basis for making judgments about the carrying values of assets, liabilities and equity and the amount of revenues and expenses. The full extent to which the COVID-19 pandemic will directly or indirectly impact our business, results of operations and financial condition, including sales, expenses, reserves and allowances, clinical trials, research and development costs and employee-related amounts, will depend on future developments that are highly uncertain, including as a result of new information that may emerge concerning COVID-19 and the actions taken to contain the pandemic or treat COVID-19, as well as the economic impact on local, regional, national and international customers and markets. We have made estimates of the impact of COVID-19 within our financial statements and there may be changes to those estimates in future periods. Actual results may differ from these 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, 2020 and 2019 consisted of investments in 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. Unrealized gains are included as a component of accumulated other comprehensive income in the consolidated balance sheets and statements of 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, 2020 and 2019, 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 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. Unrealized losses are evaluated for impairment under ASC 326, *Financial Instruments - Credit Losses*, to determine if the impairment is credit-related or noncredit-related. Credit-related impairment is recognized as an allowance on the balance sheet with a corresponding adjustment to earnings, and noncredit-related impairment is recognized in other comprehensive income, net of taxes. Evidence considered in this assessment includes reasons for the impairment, compliance with our investment policy, the severity of the impairment, collectibility of the security, and any adverse conditions specifically related to the security, an industry, or geographic area.

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, 2020 or 2019. Fair value information for these assets, including their classification in the fair value hierarchy is included in Note 4. *Fair Value Measurements***.**

There have been no changes to the valuation methods during the years ended December 31, 2020 and 2019. 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 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, 2020.

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, 2020.

Liability related to sale of future revenue

We treat the sale of future revenue to RPI as a debt financing, as we have significant continuing involvement in the generation of the cash flows. As result, we recorded the proceeds from this transaction as a liability related to the sale of future revenue to be amortized to interest expense using the effective interest rate method over the life of the arrangement.

The liability related to sale of future revenue and the related interest expense are based on our current estimates of future royalties expected to be paid over the life of the arrangement. We will periodically assess the expected royalty payments using forecasts from external sources. To the extent our future estimates of royalty payments are greater or less than previous estimates or the estimated timing of such payments is materially different than its previous estimates, we will prospectively recognize related non-cash interest expense.

For further discussion of the sale of future revenue, refer to Note 10, *Sale of Future Revenue*.

Amortization of issuance costs

We treated the liability related to sale of future revenue as a debt financing. As such, the long-term liability is initially recorded at its proceeds, net of deferred costs. Issuance costs, fees directly related to the sale of future revenue, are offset against initial carrying value of the long-term liability and are amortized on a straight-line basis over the remaining patent life of the product to an operating expense.

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 sell TIBSOVO®, our wholly owned product, to a limited number of specialty distributors and specialty pharmacy providers, 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. In addition, we receive sales order management, data and distribution services from certain Customers.
>
> Chargebacks for fees 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 include 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 and 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 January 1, 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, 2020, 2019, and 2018 were expensed prior to July 20, 2018 and, therefore, are not included in costs of sales during the years ended December 31, 2020, 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.

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, 2020 and 2019.

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, or RSUs, performance-based stock units, or PSUs, and market-based stock units, or MSUs, 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 Financial Accounting Standard Board, or FASB issued Accounting Standards Update, or ASU, No. 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 ASU 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 ASU 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.

In June 2016, the FASB issued ASU 2016-13, *Financial Instruments - Credit Losses (Topic 326)*, which introduces new guidance for the accounting for credit losses on instruments within its scope. The new guidance introduces an approach based on expected losses to estimate credit losses on certain types of financial instruments. Credit losses relating to available-for-sale debt securities will also be recorded through an allowance for credit losses rather than as a reduction in the amortized cost basis of the securities. The guidance is effective for fiscal years beginning after December 31, 2019, including interim periods within those years. The Company adopted this amendment as of January 1, 2020, which eliminated the concept of other-than-temporary impairments and required credit losses on debt securities to be recorded through an allowance for credit losses instead of as a reduction in the amortized cost basis of the securities. Application of the amendments is through a cumulative-effect adjustment to retained earnings as of the effective date. 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 4. Fair Value Measurements

The following table summarizes our cash equivalents and marketable securities measured at fair value and by level (as described in Note 3. *Summary of Significant Accounting Policies*) on a recurring basis as of December 31, 2020:

(In thousands)	Level 1	Level 2	Level 3	Total
Cash equivalents	$ 69,424	$ —	$ —	$ 69,424
Total cash equivalents	69,424	—	—	69,424
Marketable securities:				
U.S. Treasuries	—	128,809	—	128,809
Government securities	—	135,131	—	135,131
Corporate debt securities	—	279,161	—	279,161
Total marketable securities	—	543,101	—	543,101
Total cash equivalents and marketable securities	$ 69,424	$ 543,101	$ —	$ 612,525

There were no transfers between Level 1 and Level 2 and we had no financial assets or liabilities that were classified as Level 3, except for the liability related to the sale of future revenue as discussed in Note 10, *Sale of Future Revenue*, at any point during the year ended December 31, 2020.

Note 5. Marketable Securities

Marketable securities at December 31, 2020 consisted of the following:

(In thousands)	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
Current:				
U.S. Treasuries	$ 113,559	$ 134	$ (21)	$ 113,672
Government securities	108,263	37	(8)	108,292
Corporate debt securities	223,461	140	(72)	223,529
Total Current	445,283	311	(101)	445,493
Non-current:				
U.S. Treasuries	15,147	—	(10)	15,137
Government securities	26,831	8	—	26,839
Corporate debt securities	55,735	2	(105)	55,632
Total Non-current	97,713	10	(115)	97,608
Total marketable securities	$ 542,996	$ 321	$ (216)	$ 543,101

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

(In thousands)	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
Current:				
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

There were no material realized gains or losses on marketable securities for the years ended December 31, 2020 and 2019.

At December 31, 2020 and 2019, we held 87 and 113 debt securities, respectfully, that were in an unrealized loss position for less than one year. We did not record an allowance for credit losses as of December 31, 2020 and December 31, 2019 related to these securities. The aggregate fair value of debt securities in an unrealized loss position at December 31, 2020 and 2019 was $299.0 million and $345.7 million, respectively. There were no individual securities that were in a significant unrealized loss position as of December 31, 2020 and 2019. We regularly review the securities in an unrealized loss position and evaluate the current expected credit loss by considering factors such as historical experience, market data, issuer-specific factors, and current economic conditions. We do not consider these marketable securities to be impaired as of December 31, 2020 and 2019.

Note 6. Property and Equipment, net

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

(In thousands)	2020	2019
Laboratory equipment	$ 25,334	$ 23,418
Computer equipment and software	6,945	6,415
Leasehold improvements	32,568	23,879
Furniture and fixtures	3,035	2,101
Office equipment	1,651	589
Construction in progress	4,111	7,182
Total property and equipment	73,644	63,584
Less: accumulated depreciation	(41,353)	(32,112)
Total property and equipment, net	$ 32,291	$ 31,472

Depreciation expense for the years ended December 31, 2020, 2019 and 2018 was $9.4 million, $8.0 million and $7.2 million, respectively.

Note 7. Inventory

Inventory consisted of the following at December 31:

(In thousands)	2020	2019
Raw materials	$ 294	$ 180
Work-in-process	13,039	6,808
Finished goods	1,365	343
Total Inventory	$ 14,698	$ 7,331

Inventory is related to our approved product, TIBSOVO®. There were no write downs for excess and obsolete inventory during the years ended December 31, 2020, 2019 or 2018.

Note 8. Leases

Our building leases are comprised of office and laboratory space under non-cancelable operating leases. These lease agreements have remaining lease terms of seven 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.

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.

The components of lease expense and other information related to leases were as follows:

(In millions)	2020	2019
Operating Lease Costs	$ 15.2	$ 15.1
Cash paid for amounts included in the measurement of operating lease liabilities	14.4	12.8

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

We have not entered into any material short-term leases or financing leases as of December 31, 2020.

In arriving at the operating lease liabilities as of December 31, 2020, we applied the weighted-average incremental borrowing rate of 5.7% over a weighted-average remaining lease term of 7.2 years. 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, 2020, undiscounted minimum rental commitments under non-cancelable leases, for each of the next five years and total thereafter, were as follows:

(In thousands)	
2021	$ 13,198
2022	16,773
2023	18,126
2024	18,660
2025	19,507
Thereafter	44,385
Undiscounted minimum rental commitments	130,649
Interest	(26,098)
Total operating lease liabilities	$ 104,551

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 9. Accrued Expenses

Accrued expenses consisted of the following at December 31:

(In thousands)	2020	2019
Accrued compensation	$ 26,286	$ 18,982
Accrued research and development costs	14,904	21,777
Accrued professional fees	3,366	8,335
Accrued revenue-related reserves and other	15,584	4,048
Total accrued expenses	$ 60,140	$ 53,142

Note 10. Sale of Future Revenue

On June 11, 2020, we sold our tiered, sales-based royalty rights on worldwide net sales of IDHIFA®, as well as our rights to receive up to $55.0 million in outstanding regulatory milestone payments from BMS, to RPI for $255.0 million. The gross proceeds of $255.0 million approximate the fair value of the liability related to the sale of future revenue based on a discounted cash flow model. The fair value for the liability related to the sale of future revenue at December 31, 2020 was based on our current estimates of future royalties expected to be paid to RPI over the remaining patent life of the product, which are considered level 3 inputs.

Under the terms of the purchase agreement with RPI, although we sold all of our rights to receive royalties on worldwide net sales of IDHIFA® and future regulatory milestone payments, we continue to co-promote IDHIFA® and are therefore involved in the generation of these royalties. Due to our continuing involvement, we will continue to account for any royalties earned as revenue. We recorded the net proceeds from this transaction as a liability related to sale of future revenue, or the Royalty Obligation, that will be amortized using the effective interest method over the remaining patent life. Significant judgment was applied in determining the appropriate accounting treatment for the transaction.

As royalties are remitted to RPI from BMS, the balance of the Royalty Obligation will be effectively repaid over the life of the BMS license agreement. In order to determine the amortization of the Royalty Obligation, we are required to estimate the total amount of future royalty payments to RPI over the life of the BMS license agreement. The $255.0 million recorded will be accreted to the total of these royalty payments as interest expense over the life of the Royalty Obligation. At December 31, 2020, our estimate of this total interest expense resulted in an effective annual interest rate of approximately 9.5%. This estimate contains significant assumptions that impact both the amount recorded at execution and the interest expense that will be recognized over the royalty period. We will periodically assess the estimated royalty payments to RPI from BMS and to the extent the amount or timing of such payments is materially different than the original estimates, an adjustment will be recorded prospectively to increase or decrease interest expense. There are a number of factors that could materially affect the amount and timing of royalty payments to RPI from BMS, and correspondingly, the amount of interest expense recorded by us, most of which are not within our control. Such factors include, but are not limited to, delays or discontinuation of development of enasidenib, regulatory approval, changing standards of care, the introduction of competing products, manufacturing or other delays, generic competition, intellectual property matters, adverse events that result in governmental health authority imposed restrictions on the use of the drug products, significant changes in foreign exchange rates as the royalties remitted to RPI are made in U.S. dollars (USD) while the underlying sales of enasidenib will be made in currencies other than USD, and other events or circumstances that are not currently foreseen. Changes to any of these factors could result in increases or decreases to both royalty revenues and interest expense.

The following table shows the activity of the Royalty Obligation since the transaction inception through December 31, 2020:

(in thousands)	December 31, 2020
Proceeds from the sale of future revenue	$ 255,000
Issuance costs	(4,463)
Non-cash royalty related to the sale of future revenue	(7,294)
Non-cash interest expense associated with the sale of future revenue	17,832
Amortization of issuance costs	194
Liability related to the sale of future revenue	$ 261,269

During the year ended December 31, 2020, $7.3 million of non-cash royalty revenue from net sales of IDHIFA® were recognized.

Note 11. 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 12. Product Revenue

Upon FDA approval of TIBSOVO® in the U.S., on July 20, 2018, we began generating product revenue from sales of TIBSOVO®.

(In thousands)	2020	2019	2018
Product revenue, net	$ 121,089	$ 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, 2020:

(In thousands)	Contractual Adjustments	Government Rebates	Returns	Total
Balance at December 31, 2019	$ 874	$ 1,124	$ 1,798	$ 3,796
Current provisions relating to sales in the current year	14,410	13,627	1,252	29,289
Adjustments relating to prior years	(3)	122	(1,404)	(1,285)
Payments/returns relating to sales in the current year	(13,112)	(2,987)	—	(16,099)
Payments/returns relating to sales in the prior years	(653)	(677)	—	(1,330)
Balance at December 31, 2020	$ 1,516	$ 11,209	$ 1,646	$ 14,371

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

Total revenue-related reserves for the years ended December 31, 2020 and 2019 above, included in our consolidated balance sheets, are summarized as follows:

(In thousands)	December 31, 2020	December 31, 2019
Reduction of accounts receivable	$ 902	$ 540
Component of accrued expenses	13,469	3,256
Total revenue-related reserves	$ 14,371	$ 3,796

The following table presents changes in our contract assets during the year ended December 31, 2020:

(In thousands)	December 31, 2019	Additions	Deductions	December 31, 2020
Contract assets				
Accounts receivable, net [1]	$ 8,952	$ 149,207	$ (136,831)	$ 21,328

(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 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.

Note 13. 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. On June 11, 2020, we sold our tiered, sales-based royalty rights on worldwide net sales of IDHIFA®, as well as our rights to receive up to $55.0 million in outstanding regulatory milestone payments from BMS, to RPI for $255.0 million. Under the 2010 Agreement, we are eligible to receive a $25.0 million potential milestone payment for the enasidenib program upon achievement of a specified ex-U.S. commercial milestone event, as well as reimbursement for costs incurred for our co-commercialization efforts and development activities.

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. The initial four-year research term for the 2016 Agreement expired on May 17, 2020. On March 25, 2020 Celgene declined the option to extend the research agreement. Further, on April 10, 2020 Celgene notified us that they declined to elect any program as a continuation program under the 2016 agreement. Celgene had designated AG-270, our inhibitor MAT2A, as a development candidate under the 2016 Agreement. On March 25, 2020, Celgene notified us of their decision to decline their option to enter into a development & commercialization agreement with respect to the MAT2A program under the 2016 Agreement.

2016 Agreement

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, would be governed by the 2016 Agreement.

The initial four-year research term expired on May 17, 2020. On March 25, 2020 Celgene declined the option to extend the research agreement for up to two, or in specified cases, up to four additional one-year terms which would have required the payment of a $40.0 million extension fee. Further, on April 10, 2020 Celgene notified us that they declined to elect any program as a continuation program under the 2016 agreement. Celgene had designated AG-270, our inhibitor of methionine adenosyltransferase 2a, or MAT2A, as a development candidate under the 2016 Agreement. On March 25, 2020, Celgene notified us of their decision to decline their option to enter into a development & commercialization agreement with respect to the MAT2A program under the 2016 Agreement which would have required the payment of a $30.0 million fee. As a result of the decisions, the research services were fully satisfied as of May 17, 2020, no additional performance obligations remain under the 2016 Agreement and we are no longer eligible for any milestone payments for the 2016 Agreement.

During the research term of the 2016 Agreement, we conducted research programs focused on discovering compounds that are active against metabolic targets in the immuno-oncology, or IO, field. For each program under the 2016 Agreement, we could have nominated compounds that meet specified criteria as development candidates and, in limited circumstances, Celgene could also nominate compounds as development candidates for each such program. Celgene could designate the applicable program for further development following any such nomination, after which we could 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 could 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 could 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 designated for further development, and for each continuation program. Celgene could have exercised 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) which ended 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 would also subject to the exclusive options described above.

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

Under the terms of the 2016 Agreement, if Celgene had exercised their option, the parties would 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 would co-develop and co-commercialize licensed products worldwide. Either we or Celgene would lead development and commercialization of licensed products for the United States, and Celgene would lead development and commercialization of licensed products outside of the United States. Depending on the country, the parties would each have the right to provide a portion of field-based marketing activities. Under each license agreement, Celgene would 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, if Celgene had exercised their option, the parties would have 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 had the option to designate one program in the IO field as the 65/35 program, for which Celgene would be the lead party for the United States and would have a 65% profit or loss share. For programs in the IO field other than the 65/35 program, we and Celgene would 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 would book commercial sales of licensed products, if any, in the United States, and Celgene would book commercial sales of licensed products, if any, outside of the United States.

License agreements

Under each license agreement under the 2016 Agreement, Celgene would 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 provided 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. On March 25, 2020, Celgene declined the option to extend the research agreement for up to two, or in specified cases, up to four additional one-year terms. Celgene was also required to pay an $8.0 million designation fee for each program that Celgene designated for further development and for each continuation program. On April 10, 2020, Celgene notified us that they declined to elect any program as a continuation program under the 2016 agreement. 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 exercised its option to develop and commercialize, subject to antitrust clearance, Celgene would be required to 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. On March 25, 2020, Celgene notified us of their decision to decline their option to enter into a Development & Commercialization Agreement with respect to the MAT2A

program under the 2016 Agreement. In certain cases, Celgene could 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, which was not exercised during the year ended December 31, 2020. As a result of the decisions, the research services were fully satisfied as of May 17, 2020, no additional performance obligations remain under the 2016 Agreement and we are no longer eligible for any milestone payments for the 2016 Agreement.

We were 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 were 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 could 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 would have the sole right to develop, manufacture and commercialize the applicable licensed products throughout the world, at its cost, and we would 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.

Termination

The term of the 2016 Agreement commenced on May 17, 2016 and expired on May 17, 2020 in its entirety. The research services were fully satisfied as of May 17, 2020, no additional performance obligations remain under the 2016 Agreement and we are no longer eligible for any milestone payments for the 2016 Agreement.

Exclusivity

While any of Celgene's options remained available under the 2016 Agreement, subject to specified exceptions, we could 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 could 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 2010 Agreement, we received royalties at tiered, low-double digit to mid-teen percentage rates on net sales of IDHIFA®.

On June 11, 2020, we sold our tiered, sales-based royalty rights on worldwide net sales of IDHIFA®, as well as our rights to receive up to $55.0 million in outstanding regulatory milestone payments from BMS, to RPI for $255.0 million. Under the 2010 Agreement, we were eligible to receive a $25.0 million potential milestone payment for the enasidenib program upon achievement of a specified ex-U.S. commercial milestone event, as well as reimbursement for costs incurred for our co-commercialization efforts and development activities.

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 perform 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 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, 2020, there are no remaining performance obligations under the 2016 Agreement. The research services were fully satisfied as of May 17, 2020, no additional performance obligations remain under the 2016 Agreement and we are no longer eligible for any milestone payments for the 2016 Agreement.

As of December 31, 2020, the aggregate amount of the transaction price allocated to performance obligations under the 2010 Agreement that are remaining was $3.9 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)	2020	2019	2018
Services performed that were considered performance obligations upon the adoption of ASC 606			
Licenses	$ —	$ —	$ 15,000
On-going research and development services	64,347	35,954	40,575
Committee participation	—	—	—
Services performed that were not considered performance obligations as of the adoption of ASC 606			
Development activities	—	—	1,342
Commercialization Activities	3,927	3,303	3,744
Total collaboration revenue - related party	$ 68,274	$ 39,257	$ 60,661

The following table presents changes in our contract assets and liabilities during the year ended December 31, 2020:

(In thousands)	December 31, 2019	Additions	Deductions	December 31, 2020
Contract assets				
Collaboration receivable – related party [1]	$ 1,539	$ 5,610	$ (6,141)	$ 1,008
Unbilled receivable – related party [2]	—	1,821	(706)	1,115
Royalty receivable – related party [3]	2,900	5,015	(7,915)	—
Contract liabilities				
Deferred revenue – related party, current and non-current portions [4]	61,513	2,421	(63,934)	—

(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) Unbilled receivables - related party amounts relate to future reimbursable costs to Celgene.
(3) Additions to royalty receivables - related party relate to amounts billed to Celgene during the reporting period. Deductions to receivables relate to collection of receivables during the reporting period.
(4) Additions to deferred revenue - related party 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, 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.

During the years ended December 31, 2020, 2019 and 2018, we recognized the following as revenue due to changes in the contract liability balances:

(In thousands)	2020	2019	2018
Amounts included in the contract liability at the beginning of the period	$ 61,513	$ 31,605	$ 37,590
Performance obligations satisfied in previous periods	—	—	469

Royalty revenue

During the years ended December 31, 2020, 2019 and 2018, we recognized the following as royalty revenue:

(In thousands)	2020	2019	2018
Royalty revenue – related party	$ 10,262	$ 10,542	$ 7,215

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.

On June 11, 2020, we sold our tiered, sales-based royalty rights on worldwide net sales of IDHIFA®, as well as our rights to receive up to $55.0 million in outstanding regulatory milestone payments from BMS, to RPI for $255.0 million. For further discussion of the sale of future revenue, refer to Note 10, *Sale of Future Revenue*.

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 years ended December 31, 2020, and 2019 we did not receive any milestone payments related to our Collaboration Agreements, and all variable consideration relating to the remaining development, regulatory and sales-based milestones that can be earned under the terms of the 2010 Agreement remain fully constrained. On June 11, 2020, we sold our tiered, sales-based royalty rights on worldwide net sales of IDHIFA®, as well as our rights to receive up to $55.0 million in outstanding regulatory milestone payments from BMS, to RPI for $255.0 million. For further discussion of the sale of future revenue, refer to Note 10, *Sale of Future Revenue*.

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 2010 Agreement is the achievement of a specified ex-U.S. commercial milestone event. Achievement of this event will result in a milestone payment of $25.0 million under the 2010 Agreement. We remain eligible to receive this milestone payment under our purchase agreement with RPI.

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, Singapore, and Taiwan, or the CStone Territory. We retain development and commercialization rights for the rest of the world. On March 2, 2020, we amended the CStone Agreement to include Singapore as part of the CStone Territory. 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.

Pursuant to 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 the CStone Territory, 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 the CStone Territory.

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, 2020, the aggregate amount of the transaction price allocated to performance obligations that are partially unsatisfied was $0.5 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)	2020	2019	2018
Services performed that were considered performance obligations upon contract inception			
Licenses	$ —	$ 5,000	$ 12,440
Other services	192	235	—
Services performed that were not considered performance obligations upon contract inception			
Other services	3,379	3,027	230
Total collaboration revenue – other	$ 3,571	$ 8,262	$ 12,670

The following table presents changes in our contract assets during the year ended December 31, 2020:

(In thousands)	December 31, 2019	Additions	Deductions	December 31 2020
Contract assets				
Collaboration receivable – other (1)	$ 1,928	$ 3,571	$ (3,551)	$ 1,948

(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, 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.

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, 2020, no milestone payments were received. 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, 2020, no milestone payments were made. 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. During the year ended December 31, 2018, no milestone payments were made.

Note 14. 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 15. 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, RSUs, 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, 2020, the total number of shares reserved under the 2007 Plan and the 2013 Plan are 10,584,232, and we had 2,971,884 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, 2021, 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, 2020:

	Number of Stock Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding at December 31, 2019	6,201,485	$ 58.61	7.09	$ 28,528
Granted	1,004,145	49.42		
Exercised	(360,822)	20.19		
Forfeited/Expired	(701,762)	66.48		
Outstanding at December 31, 2020	6,143,046	$ 58.46	6.68	$ 13,714
Exercisable at December 31, 2020	4,117,900	$ 60.62	5.78	$ 11,791
Vested and expected to vest at December 31, 2020	6,143,046	$ 58.46	6.68	$ 13,714

The weighted-average grant date fair value of options granted was $32.10, $36.44 and $53.22 during the years ended December 31, 2020, 2019 and 2018, respectively. The total intrinsic value of options exercised was $10.4 million, $6.4 million and $65.1 million during the years ended December 31, 2020, 2019 and 2018, respectively.

At December 31, 2020, the total unrecognized compensation expense related to unvested stock option awards was $65.3 million, which we expect to recognize over a weighted-average period of approximately 2.26 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, 2020:

	Number of Stock Units	Weighted-Average Grant Date Fair Value
Unvested shares at December 31, 2019	766,953	$ 63.44
Granted	1,040,515	48.39
Vested	(332,780)	68.91
Forfeited	(190,310)	57.04
Unvested shares at December 31, 2020	1,284,378	$ 50.78

As of December 31, 2020, there was approximately $41.1 million of total unrecognized compensation expense related to RSUs, which we expect to be recognized over a weighted-average period of 1.80 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, 2020:

	Number of Stock Units	Weighted-Average Grant Date Fair Value
Unvested shares at December 31, 2019	218,143	$ 55.64
Granted	20,622	48.49
Vested	(78,920)	54.82
Forfeited	(17,616)	61.93
Unvested shares at December 31, 2020	142,229	$ 54.28

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, 2020, there was no unrecognized compensation expense related to PSUs with performance-based vesting criteria that are considered probable of achievement that we expect to recognize. There is $5.9 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, 2020:

	Number of Stock Units	Weighted-Average Grant Date Fair Value
Unvested shares at December 31, 2019	42,695	$ 41.50
Granted	—	—
Unvested shares at December 31, 2020	42,695	$ 41.50

As of December 31, 2020, there was no remaining unrecognized compensation expense related to MSUs.

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 120,293 shares and 77,981 shares during the years ended December 31, 2020 and 2019, respectively, under the 2013 ESPP. The 2013 ESPP provides participating employees with the opportunity to purchase up to an aggregate of 836,363 shares of our common stock. As of December 31, 2020, we had 471,353 shares available for future issuance under the 2013 ESPP. On January 1, 2021, 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, 2020, 2019 and 2018, 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)	2020	2019	2018
Stock options	$ 44,942	$ 48,219	$ 51,460
Restricted stock units	26,070	19,079	12,032
Performance-based stock units	1,866	2,647	8,717
Employee Stock Purchase Plan	1,463	1,437	1,148
Other stock awards	781	991	—
Total stock-based compensation expense	$ 75,122	$ 72,373	$ 73,357

Expenses related to equity-based awards were allocated as follows in the consolidated statements of operations:

(In thousands)	2020	2019	2018
Research and development expense	$ 37,147	$ 39,029	$ 41,982
Selling, general and administrative expense	37,975	33,344	31,375
Total stock-based compensation expense	$ 75,122	$ 72,373	$ 73,357

No related tax benefits were recognized for the years ended December 31, 2020, 2019 and 2018.

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:

	2020	2019	2018
Risk-free interest rate	1.24 %	2.32 %	2.71 %
Expected dividend yield	—	—	—
Expected term (in years)	6.05	6.06	6.06
Expected volatility	73.80 %	76.19 %	76.62 %

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 16. Income Taxes

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

(In thousands)	2020	2019	2018
Domestic	$ (328,813)	$ (432,535)	$ (311,159)
Foreign	1,364	21,063	(34,869)
Total	$ (327,449)	$ (411,472)	$ (346,028)

We did not have any material provision for income taxes for the years ended December 31, 2020, 2019 and 2018.

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, 2020, 2019 and 2018:

	2020	2019	2018
Income tax benefit computed at federal statutory tax rate	21.0 %	21.0 %	21.0 %
State taxes, net of federal benefit	2.5 %	2.8 %	0.8 %
Change in valuation allowance	(28.3)%	(27.2)%	(28.4)%
General business credits and other credits	7.0 %	5.0 %	5.7 %
Permanent differences and other adjustments	(1.6)%	(1.3)%	(0.7)%
Stock based compensation	(0.6)%	(0.6)%	2.2 %
Foreign rate differential	— %	0.3 %	(0.6)%
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, 2020 and 2019 are as follows:

(In thousands)	2020	2019
Deferred tax assets:		
Net operating loss carryforwards	$ 310,841	$ 294,614
Deferred revenue	—	14,372
Tax credit carryforwards	163,589	141,219
Purchased intangible assets	13,543	14,479
Stock-based compensation	34,284	30,861
Operating lease liability	25,085	27,173
Non-deductible accruals and reserves, including inventory	12,730	4,729
RPI Royalty Sale	58,048	—
Other	1,230	—
Total deferred tax assets	619,350	527,447
Depreciation and amortization	(4,002)	(2,613)
Operating lease right of use asset	(20,596)	(22,625)
Less: valuation allowance	(594,752)	(502,209)
Net deferred taxes	$ —	$ —

On March 27, 2020, the Coronavirus Aid, Relief, and Economic Security (CARES) Act was signed into law making several changes to the Internal Revenue Code. The changes include, but are not limited to: increasing the limitation on the amount of deductible interest expense, allowing companies to carryback certain net operating losses, and increasing the amount of net operating loss carryforwards that corporations can use to offset taxable income. The tax law changes in the Act did not have a material impact on the Company's income tax provision.

As of December 31, 2020, we had net operating loss carryforwards, or NOLs, available to reduce federal, state and foreign income taxes of approximately $1,201.6 million, $906.0 million and $67.0 million, respectively. If not utilized, these NOLs begin to expire in 2033 (for pre-2018 NOLs), 2032 and 2024, respectively. Approximately $738.2 million of federal NOLs can be carried forward indefinitely. At December 31, 2020, we also had available research and development tax credits for federal and state income tax purposes of approximately $36.9 million and $18.4 million, respectively. If not utilized, the credits begin to expire in 2027 for both 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, 2020, we had available orphan drug tax credits for federal purposes only of approximately $111.5 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, 2020 and determined that transactions have resulted in no ownership changes during the year ended December 31, 2020, as defined by Section 382. The impact of the historical ownership changes has been reflected in our deferred tax assets in the table above.

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 $594.8 million and $502.2 million as of December 31, 2020 and December 31, 2019, respectively, because we have determined that it is more likely than not that these assets will not be fully realized.

The following table presents our change in valuation allowance for the years ended December 31, 2020 and, 2019:

(in thousands)	2020	2019
Valuation allowance at the beginning of the year	$ 502,209	$ 390,753
Increase for the current period	92,543	111,456
Valuation allowance at the end of the year	$ 594,752	$ 502,209

As of December 31, 2020, the unremitted earnings of our foreign subsidiaries are not material. We have not provided for U.S. income taxes or foreign withholding taxes on these earnings as it is our current intention to permanently reinvest these earnings outside the U.S. The tax liability on these earnings is also not material. Events that could trigger a tax liability include, but are not limited to, distributions, reorganizations or restructurings and/or tax law changes.

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, 2020 and 2019:

(In thousands)	2020	2019
Unrecognized tax benefits at the beginning of the year	$ 17,460	$ 14,288
Gross increases - current period tax positions	3,671	3,172
Unrecognized tax benefits at the end of the year	$ 21,131	$ 17,460

We will recognize interest and penalties related to uncertain tax positions above the line as an expense to continuing operations. As of December 31, 2020 and 2019, we had no accrued interest or penalties related to uncertain tax positions and no such amounts have been recognized. If all of the Company's unrecognized tax benefits as of December 31, 2020 were to become recognizable in the future, we would record a $21.1 million of unrecognized tax benefits. Upon close of the proposed sale to Servier, we will evaluate the tax impact of the transaction. 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, Switzerland, Netherlands, Germany, Italy and France. The statute of limitations for assessment by the IRS and state tax authorities is open for tax years ending December 31, 2020, 2019, 2018, and 2017, although carryforward attributes that were generated for tax years prior to 2017 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, 2020, 2019, 2018, and 2017. The Company's subsidiaries in the Netherlands and Germany were incorporated in 2019 and therefore the statute of limitations for assessment that remain open in these jurisdictions are for the tax year ending December 31, 2020 and 2019. The Company's subsidiaries in the Italy and France were incorporated in 2020 and therefore the statute of limitations for assessment that remain open in these jurisdictions are for the tax year ending December 31, 2020. There are currently no federal, state or foreign audits in progress.

Note 17. 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 18. 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, 2020 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, 2020, 2019 and 2018.

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,		
	2020	2019	2018
Stock options	6,143,046	6,201,485	5,416,069
Restricted stock units	1,284,378	766,953	532,144
Performance-based stock units	—	72,046	169,031
Employee Stock Purchase Plan shares	46,439	49,418	32,304
Total	7,473,863	7,089,902	6,149,548

Note 19. Selected Quarterly Financial Data (Unaudited)

The following table contains quarterly financial information for 2020 and 2019:

2020 (in thousands, except per share data)	First Quarter	Second Quarter	Third Quarter	Fourth Quarter
Total revenue	$ 87,098	$ 37,347	$ 34,706	$ 44,045
Loss from operations	(43,192)	(90,196)	(90,327)	(92,434)
Net loss	(40,256)	(90,478)	(98,979)	(97,657)
Net loss per share – basic and diluted	(0.59)	(1.31)	(1.43)	(1.41)

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)

EXECUTIVE **LEADERSHIP**

Jacqualyn Fouse, Ph.D.
Chief Executive Officer

Jonathan Biller
Chief Financial Officer and Head of Legal and Corporate Affairs

Chris Bowden, M.D.
Chief Medical Officer

Bruce Car, Ph.D.
Chief Scientific Officer

Melissa McLaughlin
Chief People Officer

Darrin Miles
Chief Commercial Officer

Clive Patience, Ph.D.
EVP, Technical Operations

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Former EVP & CFO, Alexion

Ian Clark
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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 20, 2021. 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
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Agios Pharmaceuticals, Inc.
88 Sidney Street
Cambridge, MA 02139-4169

www.agios.com