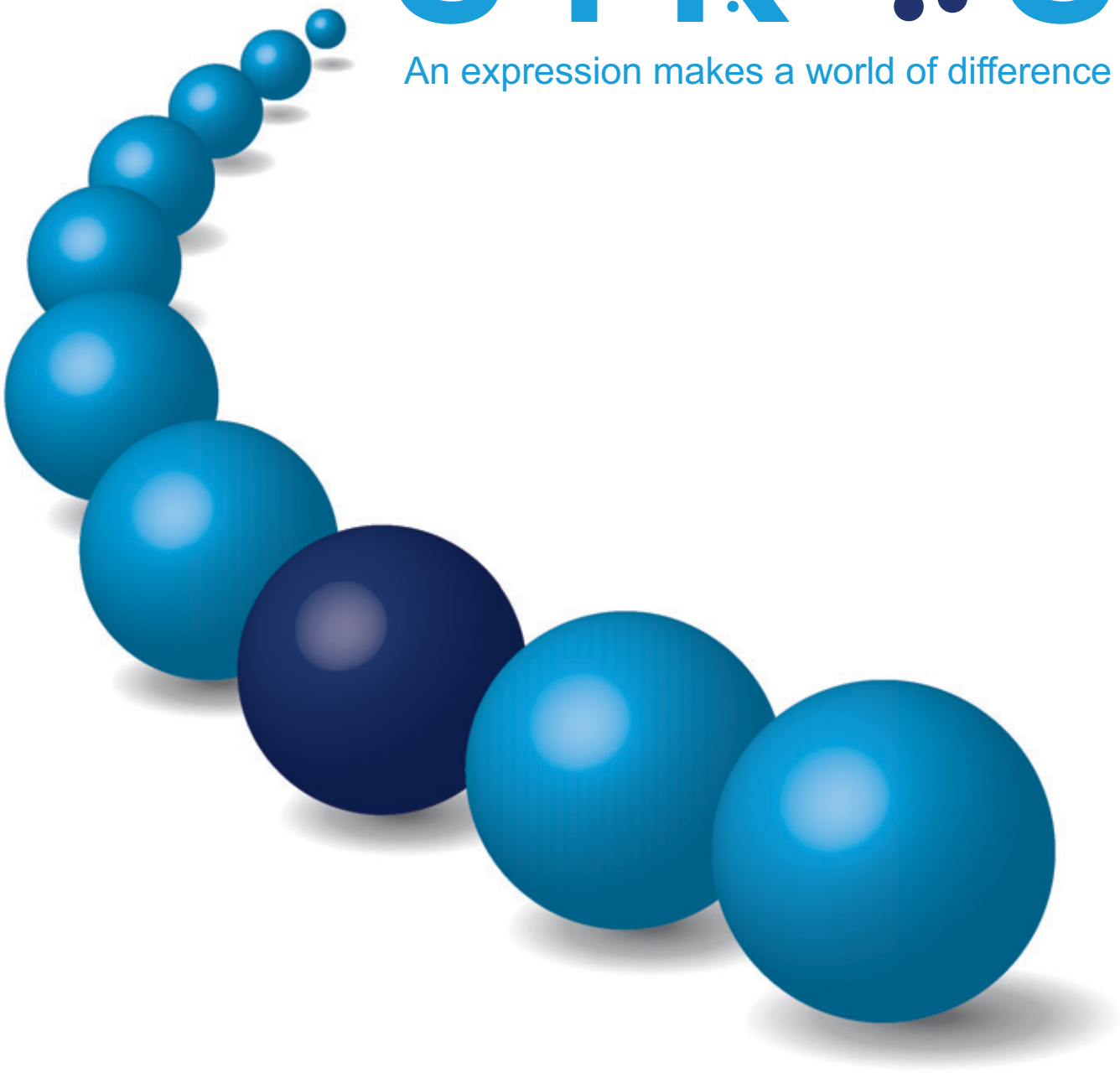
SYROS

An expression makes a world of difference



Annual Report 2019

Dear Fellow Shareholders,

In recent months, the COVID-19 pandemic has upended life as we know it. At this writing, schools across the country are closed, restaurants are shuttered, and companies are largely operating virtually. While it is a period of great uncertainty, what is clear now more than ever is the importance of our mission and the need for medical innovation.

As a company and an industry, we must continue our efforts to make a difference for people living with serious diseases. The need among patients with the cancers and monogenic diseases that we aim to treat at Syros has not changed. They face significant mortality and morbidity and are counting on breakthroughs. Even as we chart our way through these uncertain times, our commitment is unwavering: we remain focused on developing novel gene control medicines to transform patients' lives.

In 2019, we made significant progress across our pipeline. We continued to advance SY-1425, our first-in-class selective RARα agonist, in a Phase 2 clinical trial, presenting promising data in newly diagnosed unfit RARA-positive acute myeloid leukemia (AML) patients and initiating a trial cohort in relapsed or refractory RARA-positive AML patients. We built on our leadership in CDK7 inhibition, prioritizing the development of SY-5609, our highly selective and potent oral CDK7 inhibitor, now in a Phase 1 trial in select solid tumor patients. We entered into a collaboration with Global Blood Therapeutics to expand our drug discovery effort in sickle cell disease and beta thalassemia, with the aim of accelerating the development of novel oral medicines that provide a functional cure for patients with these diseases; and we named our second monogenic disease program in myotonic dystrophy type 1, a debilitating disorder caused by a defective DMPK gene.

Each of these programs has the potential to provide a profound benefit for patients. Based on the data to date, we believe SY-1425 in combination with azacitidine is highly active with a favorable tolerability profile in a subset of AML patients that we identified using our gene control platform. In newly diagnosed unfit RARA-positive AML patients, the data showed high complete response (CR) rates, deep molecular and cytogenetic CRs, rapid onset of action, and early evidence of durability, without increasing blood-related complications that are often seen when combining drugs to treat leukemia. Looking ahead to the fourth quarter of this year, we expect to report mature data from the trial cohort in these patients, as well as potential proof-of-concept data in the trial cohort in relapsed or refractory RARA-positive AML patients.

We believe that SY-5609 represents a potentially transformative targeted approach for difficult-to-treat cancers. We initiated a Phase 1 clinical trial early this year in patients with advanced breast, colorectal, lung or ovarian cancer, as well as in patients with any solid tumor harboring Rb pathway alterations. In preclinical studies, SY-5609 has shown substantial anti-tumor activity in these tumor types at doses below the maximum tolerated dose. Additionally, in models of breast, lung and ovarian cancers, deeper and more sustained responses were associated with Rb alterations. We believe focusing on these patient populations increases our chances of seeing early signals of clinical activity. We expect to report initial safety, pharmacokinetic and pharmacodynamic data from the Phase 1 dose escalation in the fourth quarter of this year, with additional dose-escalation data, including clinical activity data, expected in mid-2021.

Our progress provides a tremendous foundation for growth, and it is a testament to our people, programs and platform. While these are unprecedented times, I am confident we will adapt and continue to execute with excellence as we build Syros into an enduring company with a deep portfolio of transformative medicines.

Sincerely,

Nancy A. Simonian, M.D.
Chief Executive Officer

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 10-K

(Mark One)

☑ ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the fiscal year ended December 31, 2019

OR

☐ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from to

Commission file number 001-37813

SYROS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**45-3772460**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
35 CambridgePark Drive, 4th Floor Cambridge, Massachusetts	**02140**
(Address of principal executive offices)	**(Zip code)**

(617) 744-1340

(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of Class	Trading Symbol	Name of Exchange on Which Registered
Common Stock, $0.001 par value	SYRS	**Nasdaq Global Select Market**

Securities registered pursuant to Section 12(g) of the Act:
None.

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☑

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☑

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☑ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☑ No ☐

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

Large accelerated filer	☐	Accelerated filer	☑
Non-accelerated filer	☐	Smaller reporting company	☑
		Emerging growth company	☑

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

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

As of June 28, 2019, the last business day of the registrant's most recently completed second fiscal quarter, the aggregate market value of the registrant's common stock held by non-affiliates was $351,069,926 based on the last reported sale price of such stock on the Nasdaq Global Select Market as of such date.

Portions of the registrant's definitive proxy statement for its 2020 Annual Meeting of Stockholders, which the registrant intends to file pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year ended December 31, 2019, are incorporated by reference into Items 10, 11, 12, 13 and 14 of Part III of this Annual Report on Form 10-K. As of February 29, 2020, the registrant had 43,398,396 shares of Common Stock, $0.001 par value per share, outstanding.

TABLE OF CONTENTS

Cautionary Note Regarding Forward-Looking Statements and Industry Data

This Annual Report on Form 10-K, or Annual Report, contains forward-looking statements that involve substantial risks and uncertainties. The forward-looking statements are contained principally in the sections of this Annual Report entitled "Business," "Risk Factors," and "Management's Discussion and Analysis of Financial Condition and Results of Operations," but are also contained in other sections of this Annual Report. All statements, other than statements of historical facts, contained in this Annual Report, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of management and expected market growth are forward-looking statements. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "plan," "potential," "predict," "project," "should," "target," "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. In addition, statements that "we believe" and similar statements reflect our beliefs and opinions on the relevant subject. The forward-looking statements and opinions contained in this Annual Report are based upon information available to us as of the date of this Annual Report and, while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information.

These forward-looking statements include, among other things, statements about:

- our plans to initiate and expand clinical trials of our product candidates and our expectations for the timing, quantity and quality of information to be reported from our clinical trials of SY-1425 and SY-5609;
- planned clinical trials for our product candidates, whether conducted by us or by any future collaborators, including the timing of these trials and of the anticipated results;
- our ability to discover and develop compounds suitable for clinical development and the timing for designation of future development candidates;
- our ability to replicate in any clinical trial of one of our product candidates the results we observed in preclinical or earlier clinical studies of such product candidate;
- our plans to research, develop, seek approval for, manufacture and commercialize our current and future product candidates;
- our plans to develop and seek approval of companion diagnostic tests for use in identifying patients who may benefit from treatment with our products and product candidates;
- our expectations regarding the potential benefits of our gene control platform and our approach;
- our ability to enter into, and the terms and timing of, any collaborations, license agreements, or other arrangements;
- whether our collaboration with Incyte Corporation, or Incyte, will yield any validated targets, whether Incyte will exercise any of its options to exclusively license intellectual property directed to such targets, and whether and when any of the target validation fees, option exercise fees, milestone payments or royalties under the Incyte collaboration will ever be paid;
- whether a drug candidate will be nominated to enter investigational new drug application-enabling studies under our sickle cell disease collaboration with Global Blood Therapeutics, Inc., or GBT, whether GBT will exercise its option to exclusively license intellectual property arising from the collaboration, whether and when any option exercise fees, milestone payments or royalties under the collaboration agreement with GBT will ever be paid, and whether we exercise our U.S. co-promotion option under the GBT agreement;
- the potential benefits of any future collaboration;
- developments relating to our competitors and our industry;
- the impact of government laws and regulations;

- the timing of and our ability to file new drug applications and obtain and maintain regulatory approvals for our product candidates;
- the rate and degree of market acceptance and clinical utility of any products for which we receive marketing approval;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our intellectual property position and strategy;
- our ability to identify additional products or product candidates with significant commercial potential;
- our expectations related to the use of our current cash, cash equivalents and marketable securities and the period of time in which such capital will be sufficient to fund our planned operations; and
- our estimates regarding expenses, future revenue, capital requirements and need 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. New risks and uncertainties emerge from time to time, and it is not possible for us to predict all risks and uncertainties that could have an impact on the forward-looking statements contained in this Annual Report. We have included important factors in the cautionary statements included in this Annual Report, particularly in the "Risk Factors" section, that could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, collaborations, joint ventures or investments that we may make or enter into.

Public health epidemics or outbreaks could adversely impact our business. In December 2019, a novel strain of coronavirus emerged in Wuhan, China. While initially the outbreak was largely concentrated in China, it has now spread to several other countries and infections have been reported globally. The extent to which the coronavirus impacts our operations will depend on future developments, which are highly uncertain and cannot be predicted with confidence, including the duration and severity of the outbreak, and the actions that may be required to contain the coronavirus or treat its impact. In particular, the continued spread of the coronavirus globally, and particularly to the Cambridge, Massachusetts area, could adversely impact our operations and workforce, including our discovery research, supply chain and clinical trial operations activities, which in turn could have an adverse impact on our business and financial results.

You should read this Annual Report and the documents that we have filed as exhibits to this Annual Report 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 also 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 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 "Risk Factors" section. These and other factors could cause results to differ materially from those expressed in the estimates made by the independent parties and by us.

PART I

Item 1. BUSINESS

Overview

We are a biopharmaceutical company seeking to redefine the power of small molecules to control the expression of genes. Based on our unique ability to elucidate regulatory regions of the genome, we aim to develop medicines that provide a profound benefit for patients with diseases that have eluded other genomics-based approaches. We are currently focused on developing treatments for cancer and diseases resulting from mutations of a single gene, also known as monogenic diseases, and building a pipeline of gene control medicines.

Our lead product candidates are:

- SY-1425, a selective retinoic acid receptor alpha, or RARα, agonist that is currently being evaluated in combination with azacitidine, a hypomethylating agent frequently used to treat acute myeloid leukemia, or AML, patients in a Phase 2 clinical trial in a genomically defined subset of patients with AML; and

- SY-5609, a highly selective and potent oral inhibitor of cyclin-dependent kinase 7, or CDK7, that is currently being evaluated in the dose escalation portion of a Phase 1 clinical trial in patients with select advanced solid tumors.

In October 2019, we announced a decision to prioritize the development of SY-5609 and to discontinue further development of SY-1365, our intravenously administered CDK7 inhibitor for which we are conducting a Phase 1 clinical trial in patients with advanced solid tumors.

We also have multiple preclinical and discovery programs in oncology and monogenic diseases such as sickle cell disease and myotonic dystrophy type 1. We expect to nominate our next development candidate to enter investigational new drug application, or IND, enabling preclinical studies by the end of 2021. In December 2019, we entered into a collaboration with Global Blood Therapeutics Inc, or GBT, to discover, develop and commercialize novel therapies for sickle cell disease and beta thalassemia. We also use our gene control platform in collaboration with third parties to identify and validate targets in diseases beyond our current areas of focus. To this end, we entered into a target discovery, research collaboration and option agreement with Incyte Corporation, or Incyte in January 2018 under which we are using our platform to identify novel therapeutic targets with a focus on myeloproliferative neoplasms.

Our ongoing Phase 2 clinical trial is assessing the safety and efficacy of SY-1425 in combination with azacitidine in approximately 25 newly diagnosed AML patients who are "unfit," meaning that they are not suitable candidates for standard intensive chemotherapy, who have been prospectively selected using our proprietary RARA or IRF8 biomarkers, as well as in approximately 25 newly diagnosed unfit AML patients who are biomarker-negative. The biomarker-negative patients are being enrolled to support the development of a commercial companion diagnostic test for SY-1425. In addition, we are evaluating the safety and efficacy of SY-1425 in combination with azacitidine in approximately 25 relapsed or refractory AML patients who are being prospectively selected using the RARA biomarker.

At the European School of Haematology International Conference on AML held in October 2019, or ESH 2019, we reported data from the newly diagnosed unfit AML cohorts of the Phase 2 clinical trial as of an August 22, 2019 data cut-off. Enrollment in the newly diagnosed unfit AML cohorts of the trial is complete and we continue to follow patients in the trial. As of the data cut-off, 40 newly diagnosed unfit AML patients had been enrolled in the trial and were eligible for the safety analysis. We reported at ESH 2019 that SY-1425 in combination with azacitidine had been generally well-tolerated, with no evidence of increased toxicities due to the combination, and that adverse events had been consistent with what has previously been seen with SY-1425 and azacitidine as single agents in AML. Across all grades and causalities, the most commonly reported adverse events in these cohorts of the trial were nausea, decreased appetite, constipation, fatigue and peripheral edema, the majority of which were low grade. Of the 17 biomarker-positive patients evaluable for response, 13 were RARA-positive and four were IRF8-positive. We reported at ESH 2019 that the aggregate rate of complete response, or CR, and complete response with incomplete blood count recovery, or CRi, in each case as defined by Revised International Working Group, or IWG, criteria for AML, as of the data cut-off in RARA-positive patients was 62% and the CR rate was 54%. The duration of responses in RARA-positive patients was up to 344 days, with three of the eight responding patients having responses lasting beyond seven months at the time of the data cut-off. In patients with only the IRF8 biomarker, the CR/CRi rate was 0%, supporting our decision to use RARA as the sole biomarker for patient selection in SY-1425 clinical trials going forward. Most of the initial responses reported were seen at the end of the first treatment cycle. In 22 response-evaluable RARA-negative patients, the CR/CRi rate was 27%. Single-agent azacitidine has shown response rates of 18-29% in newly diagnosed unfit AML patients, with initial responses generally occurring after four cycles of treatment in most patients who respond. We expect to report mature data from the newly diagnosed AML cohorts of the trial, as well as potential proof-of-concept data from the relapsed or refractory AML cohort of the trial, in the fourth quarter of 2020.

In January 2020, we dosed the first patient in a Phase 1 clinical trial of SY-5609 in patients with select advanced solid tumors, including breast, colorectal, lung and ovarian cancers, and in solid tumors of any histology having retinoblastoma-pathway, or Rb pathway, alterations. The primary objectives of this trial are to assess the safety and tolerability of escalating doses of SY-5609, with the goal of establishing a maximum tolerated dose. Additional objectives include assessments of anti-tumor activity, pharmacokinetics, pharmacodynamics and potential predictive biomarkers, including Rb pathway alterations. In a future expansion portion of the Phase 1 trial, multiple cohorts are planned to further evaluate the safety and anti-tumor activity of SY-5609 as both a single agent and in combination with other therapies. We expect to report initial safety, tolerability, and pharmacokinetic and pharmacodynamic data from the trial in the fourth quarter of 2020. We also expect to report additional dose escalation data, including clinical activity data, in mid-2021.

At the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics held in October 2019, or ENA 2019, we presented preclinical data characterizing the profile of SY-5609. These data show that SY-5609 is a potent and highly selective CDK7 inhibitor, with at least 13,000-fold greater selectivity for CDK7 over closely related members of the cyclin- dependent kinase family. In addition, we reported at ENA 2019 that SY-5609 induced dose-dependent tumor growth inhibition in preclinical models of ovarian and breast cancer, tumor regressions that were sustained after the end of treatment at well-tolerated doses in multiple preclinical models of triple-negative breast, small cell lung, and high-grade serous ovarian cancers. Deeper and more sustained responses in these models were associated with the presence of Rb pathway alterations. We also reported preclinical data showing the anti-tumor activity of SY-5609 in combination with fulvestrant, a hormonal therapy, in treatment-resistant preclinical models of estrogen receptor-positive breast cancer. We have shown that SY-5609 inhibits CDK7 more potently and selectively than SY-1365, and that SY-5609 demonstrated greater tumor growth inhibition than SY-1365 in preclinical models in which both agents were studied, including models that were not responsive to SY-1365.

In October 2019, we announced data from the expansion portion of our Phase 1 clinical trial evaluating SY-1365 in multiple solid tumor indications. As of a September 30, 2019 data snapshot, 68 patients had been treated in the expansion portion of this trial, including 53 across the single-agent cohorts in patients with high-grade serous ovarian cancer, relapsed clear cell ovarian cancer, and solid tumors of any histology available for biopsy, and 15 patients in combination cohorts evaluating SY-1365 in combination with carboplatin, a chemotherapeutic agent, in patients with high-grade serous ovarian cancer and in combination with fulvestrant in patients with treatment-resistant metastatic hormone-receptor positive, or HR+, breast cancer. We initiated the single-agent expansion cohorts at a dose of 80 mg/m^2 twice weekly and the combination cohorts at 53 mg/m^2 once weekly after having observed data from the dose-escalation portion of the trial demonstrating dose-dependent effects on CDK7 occupancy and downstream gene expression changes in blood cells as well as a confirmed partial response in one patient with recurrent clear cell ovarian cancer. During the expansion portion of the trial, adverse events occurring around the time of infusion of SY-1365, which we believe to be related to the intravenous administration of SY-1365, prompted us to evaluate lower doses in the single-agent cohorts and extended infusion times across all of the cohorts. We refer to adverse events occurring around the time of infusion as peri-infusional adverse events. Extended infusion times reduced peak drug concentrations while maintaining CDK7 target occupancy and appeared to reduce the overall frequency and severity of these peri-infusional adverse events, including headache, nausea and vomiting. The best response observed across the expansion cohorts of the trial was stable disease, as defined by Response Evaluation Criteria in Solid Tumors, or RECIST, criteria. Of the 31 response-evaluable patients treated with SY-1365 as a single agent, 13 of them, or 42%, had stable disease. Of the 11 response-evaluable patients treated in the combination cohorts of the trial, seven of them, or 64%, had stable disease. Based on preclinical and clinical data generated to date, we believe that sustaining the level of CDK7 target coverage needed to enhance clinical activity with SY-1365 would require more frequent dosing, or a higher dose that would necessitate lengthening the infusion time to manage tolerability. We believe that either approach could create an overly burdensome dosing regimen for patients that could be better addressed with an oral agent like SY-5609. This belief, coupled with the superior preclinical data generated with SY-5609 relative to SY-1365 and a competitive landscape in oncology increasingly focused on oral agents, led us to make a portfolio decision to discontinue further development of SY-1365 and prioritize the development of SY-5609.

Our Focus – Gene Control Medicines Providing a Profound Benefit for Patients

There are approximately 200 different cell types in the human body. Despite having identical genomes, each of these cell types has a different function. For example, a skin cell functions differently than a muscle cell despite sharing the exact same DNA. What determines cell type and function is the specific set of genes that is expressed, or turned “on” or “off,” in that given cell. This coordinated activation and repression of genes, known as the cell’s gene expression program, is controlled in part by a number of cellular components acting on non-coding regions of the genome. These components include transcription factors, transcriptional kinases, other transcriptional and regulatory proteins, and RNA. These transcriptional and regulatory proteins bind with specific regions of non-coding DNA to control the rate and magnitude of gene transcription.

In some diseases, alterations in the physical state or function of the non-coding regions of the genome can change a cell's gene expression program, altering the type and function of that cell. Because the altered gene expression program is implemented by transcription factors, transcriptional kinases, other transcriptional and regulatory proteins, and RNA, these proteins and RNA can be important points for therapeutic intervention. Because this biology is fundamental to the function of all cells, it applies across diseases, whether the cause is genetic, environmental, bacterial, viral or multi-factorial.

Although researchers have long believed that alterations in non-coding regions of DNA, which account for 98% of the genome, play a key role in driving disease, the scientific community has lacked the tools to study these regions of the genome, rendering them poorly understood. As a result, the discovery and development of targeted therapies to date has focused almost exclusively on abnormal proteins resulting from genetic alterations found in regions of DNA that encode for proteins, which represent less than 2% of the entire genome.

We believe we have the industry-leading platform for the systematic and efficient analysis of non-coding regions of the genome to identify alterations in gene expression programs that represent optimal points of therapeutic intervention and the development of drugs to control the expression of disease-driving genes. By doing so, we believe our gene control platform will allow us to (i) identify a wide array of potential new drug targets across a range of diseases, (ii) provide a new lens for diagnosing and segmenting patients, including those with complex, multi-factorial diseases that have eluded segmentation with other genomic-based approaches, and (iii) advance a new wave of medicines that have the potential to influence multiple drivers of disease through a single target, making them less susceptible to drug resistance and providing patients with a more profound and durable benefit than many of today's targeted therapies.

Our Gene Control Platform

Our proprietary gene control platform consists of two fundamental pillars:

- identifying gene control targets that, when modulated with a drug, may provide a therapeutic benefit to defined patient populations; and
- drugging gene control targets.

We analyze gene expression programs and the non-coding regions of the genome associated with those expression programs in diseased and healthy cells taken from patient tissues to identify points of therapeutic intervention and associated biomarkers in specific patient populations. The discovery and validation of these gene control targets has led to the identification of our clinical candidates SY-1425 and SY-5609 as well as additional novel product candidates in earlier stages of research and preclinical development. We plan to analyze gene expression programs in other cancers, and to collaborate with third parties such as Incyte to identify and validate targets in diseases beyond our current areas of focus.

In some diseases, particularly monogenic diseases, research has revealed that a therapeutic benefit might be possible from modulating expression of a specific gene. We are also using our platform to characterize the regulatory region associated with such a gene and identify protein, RNA or DNA components that could be modulated to alter the expression of that single gene. We are applying this approach to sickle cell disease based on the hypothesis that increased expression of the fetal hemoglobin gene in individuals with sickle cell disease could be therapeutically beneficial, and to myotonic dystrophy type 1 based on the hypothesis that decreasing the expression of the mutated dystrophia myotonica protein kinase, or DMPK, gene would address the underlying biology of the disease.

We develop product candidates to modulate gene control targets through internal drug discovery efforts focused on creating small molecule drugs targeting transcription factors, transcriptional kinases and other transcriptional and regulatory proteins. We have also used our platform to link existing drugs to novel genomically defined patient populations, and seek to in-license, acquire or use those drugs as starting points for our own drug discovery programs to accelerate our development path, as we did with SY-1425.

We have developed significant core internal capabilities in small molecule chemistry, biochemistry and structural biology to characterize the structure and function of transcription factors such as transcriptional kinases, chromatin regulators, and other transcriptional and regulatory proteins in order to generate novel chemical matter, including SY-1365 and SY-5609. We have also developed a sophisticated suite of proprietary assays, which are internally developed tests to measure the biochemical, biophysical, cellular and genomic activity of known and novel compounds against gene control targets.

Our Clinical and Preclinical Programs

SY-1425

Overview

SY-1425 (tamibarotene) is an oral, potent and selective agonist of the transcription factor RARα. We are currently conducting a Phase 2 clinical trial assessing the safety and efficacy of SY-1425 in combination with azacitidine in approximately 25 newly diagnosed AML patients who are "unfit," meaning that they are not suitable candidates for standard intensive chemotherapy, who have been prospectively selected using our proprietary RARA or IRF8 biomarkers, as well as in approximately 25 newly diagnosed unfit AML patients who are biomarker-negative. The biomarker-negative patients were enrolled to support the development of a commercial companion diagnostic test for SY-1425. In addition, we are evaluating the safety and efficacy of SY-1425 in combination with azacitidine in approximately 25 relapsed or refractory AML patients who are being prospectively selected using the RARA biomarker. Enrollment in the newly diagnosed unfit AML cohorts of the trial is complete and we continue to follow patients in the trial. We expect to report mature data from the newly diagnosed AML cohorts of the trial, as well as potential proof-of-concept data from the relapsed or refractory AML cohort of the trial, in the fourth quarter of 2020.

Linking SY-1425 to Novel Patient Populations

We leveraged our platform to analyze gene expression programs in primary AML and breast cancer patient tissue samples. We discovered that RARA, the gene that codes for RARα, was associated with a super-enhancer in some patients' tumors but not in others. A super-enhancer is a highly specialized region of non-coding DNA central to controlling the expression of genes most crucial to the function of a given cell. The function of RARα differs depending on whether it is bound to its ligand. In the absence of a ligand, RARα represses differentiation. We believe that the RARA-associated super-enhancer drives increased expression of RARα in tumors with the super-enhancer, which leads to an abundance of unliganded RARα that results in the repression of differentiation, thereby locking the cell in an immature, proliferative and undifferentiated state. Introducing a RARα agonist, such as SY-1425, simulates the activity of a ligand, activating differentiation.

SY-1425 Development Plan

We plan to develop SY-1425 in North America and Europe for treatment of AML in genomically defined subsets of patients with the RARA biomarker. In September 2016, we initiated a multi-center, open-label Phase 2 clinical trial enrolling genomically-defined subsets of patients with AML and myelodysplastic syndrome, or MDS, pursuant to an IND accepted by the U.S. Food and Drug Administration, or FDA, in May 2016. An investigational device exemption for the assay being used to select patients with the RARA biomarker for inclusion in this trial has been approved by the FDA. Based on data from 350 patients screened as of September 2019 in our Phase 2 clinical trial, we believe approximately 30% of AML patients are positive for the RARA biomarker.

Tamibarotene, the active pharmaceutical ingredient of SY-1425, has been extensively studied and has a well-established safety profile. In our Phase 2 clinical trial, we are using the same dosage used in the treatment of acute promyelocytic leukemia, or APL, in Japan (6 mg/m^2 orally, divided into two daily doses). This same dosage for SY-1425 was previously used in a U.S. trial in relapsed and refractory APL, for which an IND was opened. We have exclusively in-licensed from TMRC Co., Ltd., or TMRC, certain intellectual property rights controlled by TMRC and the preclinical data package that was used for approval in Japan and the IND filing in the United States for use in all cancer indications in North America and Europe.

We have entered into an agreement with a third-party commercial provider to provide a validated laboratory test under Clinical Laboratory Improvement Amendment, or CLIA, guidelines using a well-established diagnostic platform and approach that is being used to prospectively enroll RARA biomarker-positive patients in our clinical trial. This CLIA laboratory test could become the basis for a commercial companion diagnostic. We are evaluating commercial providers to lead the development of a potential commercial companion diagnostic for this biomarker, but we have not yet selected a platform for development of a companion diagnostic test or entered into a definitive agreement with a third party for this work. We expect to do so in 2020.

We have chosen AML as our lead indication for development of SY-1425 due to high levels of observed activity of SY-1425 in our preclinical models, the clinical activity and tolerability observed in our Phase 2 clinical trial, the significant unmet medical need of these patients and our belief, in the case of development in relapsed or refractory AML, in the potential for efficient or accelerated development. We believe that the data being generated in the clinical trial of SY-1425 in combination with azacitidine for the treatment of RARA-positive patients with AML, if positive, could support a decision to enter into a registration-enabling clinical trial. We intend to pursue additional AML patient populations and additional indications upon establishing proof-of-concept in AML because we believe there are subsets of patients with other tumor types with the RARA biomarker.

SY-1425 in Combination with Azacitidine

In October 2018, we published preclinical data in *Haematologica*, a peer-reviewed journal of the European Hematology Association, demonstrating the mechanistic rationale for combining SY-1425 with hypomethylating agents such as azacitidine in AML with high RARA expression. These data showed that SY-1425 in combination with azacitidine resulted in synergistic anti-proliferative effects supported by evidence of DNA damage and apoptosis and, in patient-derived xenograft models of AML with high RARA expression, SY-1425 in combination with azacitidine showed both greater clearance of tumor cells in bone marrow and other tissues and greater duration of response, compared to either azacitidine or SY-1425 alone.

Our ongoing Phase 2 clinical trial is currently assessing the safety and efficacy of SY-1425 in combination with azacitidine in a fully-enrolled cohort of approximately 25 newly diagnosed unfit AML patients. The primary endpoint for this cohort of the trial is overall response rate, as determined by IWG criteria. Secondary endpoints include duration of response as well as safety and tolerability. All patients enrolled in this cohort of the trial in support of our primary efficacy analyses were prospectively selected using our proprietary RARA or IRF8 biomarkers. In addition, to support the development of a commercial companion diagnostic test for SY-1425, we are evaluating SY-1425 in combination with azacitidine in a fully-enrolled cohort of approximately 25 newly diagnosed unfit AML patients who are biomarker-negative.

At ESH 2019, we presented data from the newly diagnosed unfit AML cohorts of the trial. All patients in these cohorts of the trial were treated with azacitidine at standard daily doses of 75 mg/m^2 intravenously or subcutaneously for seven days, followed by SY-1425 administered at 6 mg/m^2/day orally, divided in two doses, for the remainder of each 28-day treatment cycle. As of an August 22, 2019 data cut-off, 40 newly diagnosed unfit patients had been enrolled in the trial and were eligible for the safety analysis. The median age of patients enrolled in these cohorts of the study was 76. Of the 17 biomarker-positive patients evaluable for response, 13 were RARA-positive and four were IRF8-positive. The data presentation at ESH 2019 included the following:

- SY-1425 in combination with azacitidine was generally well-tolerated with no evidence of increased toxicities beyond what is seen with either SY-1425 or azacitidine alone;

- the majority of non-hematologic adverse events, or AEs, were low grade, and rates of myelosuppression, including neutropenia, were comparable to reports of single-agent azacitidine in this AML population. Across all grades and causalities, the most commonly reported AEs were nausea (38%), decreased appetite (33%), constipation (33%), fatigue (33%) and peripheral edema (30%). The most commonly reported grade 3 or higher AEs of all causality were thrombocytopenia (25%), anemia (23%) and febrile neutropenia (23%); and

- the aggregate CR/CRi rate was 62% in RARA-positive patients. The CR rate in RARA-positive patients was 54%, consisting of seven CRs, including three molecular CRs and three cytogenetic CRs. Most of the initial responses were seen at the end of the first treatment cycle. The duration of these responses in RARA-positive patients was up to 344 days, with three of the eight responding patients having responses lasting beyond seven months at the time of the data cut-off. 82% of RARA-positive patients achieved or maintained transfusion independence. Responses were seen in RARA-positive patients across AML risk groups, including patients with mutations that are typically associated with poor outcomes.

- in patients with only the IRF8 biomarker, the CR/CRi rate was 0%, which led to our decision to use RARA as the sole biomarker for patient selection in SY-1425 clinical trials going forward.

- in the 22 response-evaluable RARA-negative patients, the CR/CRi rate was 27%. In the reported literature, single-agent azacitidine has shown response rates of 18-29% in newly-diagnosed unfit AML patients.

Based on analysis of third-party registry data on RARα expression and survival in AML patients, as well as our analysis of AML patient samples using our platform, we do not believe that RARA is a prognostic biomarker in AML, nor do we believe that RARA enriches for genes that may be associated with responsiveness to azacitidine. Therefore, we believe that the difference in the observed overall response rates as of the cut-off date supports the potential predictive value of the RARA biomarker for identifying newly diagnosed unfit AML patients most likely to respond to SY-1425.

Enrollment in the newly diagnosed unfit AML cohorts of the trial is complete and we continue to follow patients in the trial. We expect to report mature clinical data from these cohorts of the trial in the fourth quarter of 2020.

We are currently enrolling patients in a study cohort evaluating SY-1425 in combination with azacitidine in approximately 25 RARA-positive patients with relapsed or refractory AML and expect to report potential proof-of-concept data from this study cohort in the fourth quarter 2020. The primary endpoint for this cohort of the trial is overall response rate, as determined by IWG criteria. Secondary endpoints include duration of response as well as safety and tolerability. We expect to report potential proof-of-concept data from this cohort of the trial in the fourth quarter of 2020.

SY-1425 in Combination with Daratumumab

We reported data at the American Society of Hematology Annual Meeting held in December 2018, or ASH 2018, from a pilot cohort of our Phase 2 clinical trial of SY-1425 evaluating the safety and efficacy of SY-1425 in combination with daratumumab, an anti-CD38 antibody approved for the treatment of multiple myeloma, in biomarker-positive patients with relapsed or refractory AML or higher-risk MDS. While CD38 is normally expressed at high levels on multiple myeloma cells, AML cells typically have relatively low CD38 expression. In preclinical studies, we showed that SY-1425 induced CD38 expression in AML cells, sensitizing them to treatment with daratumumab. Patients in this cohort of the trial were treated with SY-1425 as a single agent for seven days, after which daratumumab was added and administered weekly at 16 mg/kg intravenously for eight doses, then biweekly for eight doses and every four weeks thereafter. The primary endpoint for this cohort of the trial was overall response rate, as determined by IWG criteria. Secondary endpoints included duration of response, hematologic improvement and CD38 induction, as well as safety and tolerability.

As of an October 29, 2018 data cut-off, nine patients had been enrolled in this cohort of the trial, all of them were evaluable for safety and CD38 induction, and six of them were also evaluable for clinical responses. The median age of these patients was 68, with more than half having poor risk cytogenetics. The data presentation at ASH 2018 included the following:

- SY-1425 in combination with daratumumab was generally well-tolerated with no evidence of increased toxicities;
- AEs were consistent with what has previously been seen with SY-1425 when administered as a single agent in AML and MDS patients or with daratumumab administered as a single agent in multiple myeloma patients;
- across all grades and causalities, the most commonly reported AEs were febrile neutropenia (67%), anemia (44%), nausea (44%), vomiting (44%) and infusion-related reaction (44%). The most commonly reported grade 3 or higher AEs of all causality were febrile neutropenia (67%) and anemia (44%); and
- eight of the nine (89%) patients had increased CD38 expression in myeloid blast cells, with a median 1.57-fold induction after seven days of treatment with SY-1425 as measured by mean fluorescence intensity; however, CD38 expression increased to levels exceeding those of a multiple myeloma cell line control in only two of those patients. Of those patients, one had a morphologic leukemia-free state, or MLFS, response and the other progressed without a clinical response.

In January 2019, we reported that we made a portfolio prioritization decision not to pursue further development of SY-1425 in combination with daratumumab beyond completion of this pilot cohort, which is closed to further enrollment.

SY-1425 as a Single Agent

At the American Society of Hematology Annual Meeting held in December 2017, or ASH 2017, we presented clinical data from cohorts of our Phase 2 clinical trial evaluating SY-1425 as a single agent in 29 patients with relapsed or refractory AML or relapsed higher-risk MDS, and in 29 patients with lower-risk transfusion-dependent MDS. In these cohorts of the trial, we observed that chronic daily dosing of SY-1425 administered at 6 mg/m^2 orally divided in two doses was generally well-tolerated, with a median treatment duration of 80 days and patients treated up to eight months and remaining on study. The majority of adverse events observed in the trial were low grade. At the time of the data cut-off for presenting data at ASH 2017, 48 patients were evaluable for response assessment, including 23 patients in the relapsed or refractory AML or relapsed higher-risk MDS cohort and 25 patients in the lower-risk transfusion-dependent MDS cohort. Myeloid differentiation was observed in the bone marrow, consistent with the underlying mechanism of action. Clinical activity was observed in ten of 23 (43%) evaluable patients with relapsed or refractory AML and higher-risk MDS, and two of the 25 (8%) evaluable lower-risk MDS patients. We are no longer evaluating SY-1425 as a single agent in patients with AML or MDS, but we believe that these data support the ongoing development of SY-1425 as a combination agent.

Prior Clinical Data in APL

Tamibarotene, the active pharmaceutical ingredient of SY-1425, is approved and marketed in Japan under the brand name Amnolake® for treatment of acute recurrent or intractable APL. Given the demonstrated efficacy of the drug in acute recurrent or intractable APL, we have the opportunity to evaluate SY-1425 for treatment of APL in North America and Europe, but we do not have any current plans to do so. Extensive clinical work had been conducted on tamibarotene prior to us in-licensing it from TMRC. The effectiveness of tamibarotene has been evaluated in patients with APL, including for relapsed patients and as maintenance therapy for newly diagnosed patients.

- In a Phase 2 clinical trial of tamibarotene as a single agent in patients who relapsed following treatment with all-trans retinoic acid, or ATRA, 58% achieved a complete response. The majority of these patients went on to receive a bone marrow transplant or chemotherapy after treatment with tamibarotene and maintained a complete response for at least 14 months.

- In a Phase 3 clinical trial comparing tamibarotene as an add-on therapy to arsenic trioxide, or ATO, a standard of care treatment for APL, versus ATRA as an add-on therapy to ATO in relapsed patients, patients in the tamibarotene-treated group demonstrated:

- An overall complete response rate of 80%, compared to 54% in the ATRA-treated group (p=0.022); and

- A complete molecular remission rate of 23%, compared to 3% in the ATRA-treated group (p=0.0275). Complete molecular remission is achieved when there is no evidence of disease in the patient's blood cells as detected by DNA-based tests.

- In a different Phase 3 clinical trial comparing tamibarotene to ATRA as maintenance therapy in newly diagnosed APL patients, the seven-year relapse-free survival rate in high-risk patients treated with tamibarotene was 89%, compared to 62% in high-risk patients treated with ATRA (p=0.034). In all patients, the seven-year relapse-free survival rate was 93% in the tamibarotene arm and was 84% in the ATRA arm (p=0.031).

In all these studies, tamibarotene was generally well tolerated. Adverse effects included mild or moderate dry skin, skin rash, headache and bone pain, as well as retinoic acid syndrome and elevated levels of cholesterol, lipids, liver function enzymes and white blood cells, which were severe in certain cases. One such adverse effect, retinoic acid syndrome, is referenced on the drug's label and was infrequently observed clinically. Retinoic acid syndrome is a side effect associated with retinoids and ATO and can be mitigated by regular monitoring of clinical parameters, including white blood cell counts. A summary of four published clinical studies of tamibarotene use in APL is provided below.

Design	No. Patients	Patient Population	Tamibarotene Treatment	Efficacy / Duration
Phase 2 in relapsed APL[1]	25	Relapse after ATRA-induced CR	6 mg/m^2 daily, discontinued at CR	CR = 58% (14/24 evaluable) (≥ 14 months duration in 5 patients in conjunction with BMT, 7 patients in conjunction with CT)
Phase 3 tamibarotene vs. ATRA as APL maintenance[2]	134	Front-line following ATRA-induced CR and consolidation	Tamibarotene 6 mg/m^2 vs. ATRA 45 mg/m^2 14 days every 3 months for 2 years	Overall 7-year RFS: 93% v. 84%; 7-year RFS in high risk: 89% vs. 62% (tamibarotene vs. ATRA)
Phase 2 in relapsed/refractory APL after ATRA and ATO[3]	14	Patients with prior lines of treatment (9 with 2 prior lines, 3 with 3 prior lines and 2 with 5 prior lines)	6 mg/m^2 daily for 56-day induction period then every other month as consolidation for up to one year	CR = 36% CRi = 29% mEFS = 3.5 months mOS = 9.5 months
Phase 3, tamibarotene vs. ATRA as add-on to ATO in relapsed APL[4]	71		6 mg/m^2/day tamibarotene, 25 mg/ m^2/day ATRA add-on to 0.15 mg/kg/day ATO for 56 days	**Tamibarotene +ATO** / **ATRA + ATO** CR 80% / 54% CRm 23% / 3%

Table legend:

CR = complete remission | CRm = complete molecular remission | CRi = complete remission with incomplete blood count recovery
RFS = relapse-free survival | *mEFS = median event-free survival* | *mOS = median overall survival*
BMT = bone marrow transplant | *CT = chemotherapy*

1. Tobita, et al. *Blood*, August 1997.
2. Takeshita, et al. American Society of Hematology presentation, December 2017.
3. Sanford D, et al. *British Journal of Haematology*, July 2015.
4. Wang et al, American Society of Hematology presentation, December 2015.

SY-1425 Market Opportunity

We believe that SY-1425 has the potential to address significant unmet medical need across a range of blood cancers and solid tumors and, despite a significant number of new product approvals in AML since 2018, that there continues to be a significant unmet medical need in that indication.

We believe that approximately 30,000 patients are diagnosed with AML each year in the United States and the five largest European countries (France, Germany, Italy, Spain and the United Kingdom) and estimate that sales of biopharmaceutical products for use in AML in those countries will exceed $1 billion in 2020. Based on data from 350 patients screened as of September 2019 in our Phase 2 clinical trial, we believe approximately 30% of AML patients are positive for the RARA biomarker.

It is estimated that more than half of newly diagnosed AML patients are elderly or unfit for treatment with intensive therapies, underscoring the need for well-tolerated therapies that can be used in combination. Despite initial responses to therapy in select patients, the majority of AML patients relapse or become refractory to current treatment options. There are an estimated 25,000 cases of relapsed or refractory AML each year in the United States and the five largest European countries. In the absence of adequate therapies, these relapsed or refractory patients may be put into clinical trials for new and emerging therapies, and average survival of these patients is estimated to be less than six months.

There have been no new drug approvals for higher-risk MDS since 2006. Based on current treatment guidelines, a majority of higher-risk MDS patients receive hypomethylating agents upon diagnosis, but those treatments are believed to have modest efficacy, with an estimated survival of less than 1.6 years for higher-risk, newly-diagnosed patients and less than six months for patients who have relapsed or become refractory to front-line treatment.

There are an estimated 2,000 new APL cases diagnosed in the United States and the five largest European countries each year. Despite advances in treating APL, approximately 10-20% of APL patients relapse and require salvage therapy.

SY-5609

Overview

SY-5609 is a highly potent and selective small molecule CDK7 inhibitor that can be administered orally. CDK7, a member of the cyclin-dependent kinase, or CDK, family, is a transcriptional kinase that plays a central role in the two processes that cancer cells use to survive and thrive: increased expression of cancer-promoting genes, and uncontrolled cell cycle progression. CDK7 activity has been implicated in a range of solid tumors. We believe that inhibiting CDK7 preferentially lowers the expression of disease-driving transcription factors and anti-apoptotic proteins, resulting in the preferential killing of cancer cells over non-cancerous cells. We also believe that selective inhibition of CDK7 interferes with cancer-driving adaptations at multiple points in the cell cycle, promoting the induction of apoptosis, or cell death. Using our platform, we have generated several potent and selective small molecule CDK7 inhibitors, including SY-5609.

SY-5609 Clinical Development Plan

In January 2020, we dosed the first patient in a Phase 1 clinical trial of SY-5609 in patients with breast, colorectal, lung or ovarian cancers, or with solid tumors of any histology having Rb pathway alterations. The primary objectives of this trial are to assess the safety and tolerability of escalating doses of SY-5609, with the goal of establishing a maximum tolerated dose. Additional objectives include assessments of anti-tumor activity, pharmacokinetics, pharmacodynamics and potential predictive biomarkers, including Rb pathway alterations. In a future expansion portion of the Phase 1 trial, multiple cohorts are planned to further evaluate the safety and anti-tumor activity of SY-5609 as both a single agent and in combination with other therapies. We expect to report initial safety, tolerability, and pharmacokinetic and pharmacodynamic

data from the trial in the fourth quarter of 2020. We also expect to report additional dose escalation data, including clinical activity data, in mid-2021.

Our Preclinical Data

Our clinical development program for SY-5609 is based on a robust preclinical development program in which SY-5609 has shown substantial anti-tumor activity, including complete regressions, in preclinical models of solid tumors, including breast, colorectal, lung and ovarian cancers.

At the American Association for Cancer Research Annual Meeting held in April 2019, or AACR 2019, we reported the results of a series of preclinical studies to characterize the *in vitro* and *in vivo* profile of SY-5609. The data showed that SY-5609:

- demonstrated 13,000- to 49,000-fold greater selectivity for CDK7 over other CDK family members, including CDK2, CDK9 and CDK12;
- induced robust tumor growth inhibition effects and cell cycle arrest in triple-negative breast cancer, or TNBC, and ovarian cancer cell lines at low nanomolar drug concentrations, with apoptosis, or cell death, demonstrated in cancer cells but not in non-cancerous cells;
- significantly impacted tumor growth *in vivo*, with complete regressions observed with SY-5609 as a single agent in multiple TNBC and ovarian cancer cell-line xenograft models at doses below the maximum-tolerated dose;
- demonstrated substantial tumor growth inhibition in multiple TNBC and ovarian cancer patient-derived xenograft models, with minimum weight loss observed; and
- led to decreases in CDK7 downstream protein markers, including MCL1, in treated tumor tissue, confirming CDK7 inhibition *in vivo*.

At ENA 2019, we presented additional preclinical data characterizing the profile of SY-5609. These data showed that SY-5609 induced:

- dose-dependent tumor growth inhibition in preclinical models of ovarian and breast cancer, with tumor regressions observed at doses as low as one-fifth of the maximum tolerated dose;
- rapid, sustained and dose-dependent transcriptional pharmacodynamic responses in xenograft tumor tissue that correlated with tumor growth inhibition;
- substantial tumor growth inhibition in 100% (12/12) of TNBC, small cell lung cancer and high grade serous ovarian models tested, including deep and sustained regressions in 58% (7/12) of those models, at well-tolerated doses. Rb pathway alterations were associated with these deeper and more sustained responses; and
- robust anti-tumor activity in combination with fulvestrant, a hormonal therapy, in treatment-resistant models of estrogen receptor-positive breast cancer, including models that were resistant to both fulvestrant and a CDK4/6 inhibitor.

The data presented at ENA 2019 also suggest that SY-5609 plasma exposures are dose proportional and do not accumulate with repeated daily dosing at therapeutic doses, and that the overall pharmacokinetic profile of SY-5609 supports a daily dosing regimen.

CDK7 Portfolio Prioritization

In May 2017, we began enrolling patients in a Phase 1 clinical trial of SY-1365, a potent and selective, covalent CDK7 inhibitor that is administered intravenously, in patients with advanced solid tumors. The trial evaluated the safety and tolerability of escalating doses of SY-1365 with the goal of establishing a maximum tolerated dose and a recommended Phase 2 dose and schedule. Additional study objectives included assessments of pharmacodynamic changes and early signs of biological activity using biomarkers and clinical efficacy as measured by response rate using radiographic measures.

At the EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium held in November 2018, or ENA 2018, we reported data as of October 15, 2018 from the dose-escalation portion of the Phase 1 clinical trial of SY-1365. In total, 32 patients were treated with SY-1365 as a single agent at doses ranging from 2 mg/m^2 to 112 mg/m^2 using either a weekly or twice weekly dosing regimen. Patients had a range of solid tumors, with the most prevalent being ovarian cancer (eight patients), breast cancer (eight patients) and endometrial cancer (five patients). Patients' median age was 63 (ranging from 25 to 87), with a median of five prior therapies (ranging from one to 13). As of the data cut-off, the median treatment duration was 46.5 days (ranging from two to 147 days) and four patients remained on treatment. The data presented at ENA 2018 included the following:

- AEs were predominantly low-grade, reversible and generally manageable, with the most commonly reported AEs being headache, nausea, vomiting and fatigue. No neutropenia was reported. Dose limiting toxicities were headache, coronary vasospasm and fatigue, and a maximum tolerated dose was not defined;

- SY-1365 demonstrated dose-dependent effects on CDK7 occupancy and downstream gene expression changes in blood cells. CDK7 occupancy in blood cells was similar to target occupancy in tumor tissue biopsies available from two patients in the clinical trial; and

- clinical activity measured using RECIST criteria was observed in seven of the 19 patients (37%) who were evaluable for clinical responses, including (i) one patient with recurrent ovarian clear cell cancer in her fourth relapse who had a confirmed partial response, or PR, of an approximately 32% reduction in target lesions, after two cycles of treatment at the 80 mg/m^2 twice weekly dose, who remained in PR with a 49% decrease in target lesions after her sixth cycle of treatment, and (ii) six additional patients who had stable disease lasting between 50 and 127 days, most of whom received doses greater than or equal to 32 mg/m^2.

Based on these data, we initiated the expansion portion of the Phase 1 clinical trial in September 2018. In this portion of the trial, we evaluated the safety and anti-tumor activity of SY-1365 in multiple ovarian and breast cancer populations based on supporting preclinical data, mechanistic rationale, and unmet medical need. In October 2019, we announced data from the expansion portion of our Phase 1 clinical trial of SY-1365. As of a September 30, 2019 data snapshot, 68 patients had been treated in the expansion portion of this trial, including 53 across the single-agent cohorts in patients with high-grade serous ovarian cancer, relapsed clear cell ovarian cancer, and solid tumors of any histology available for biopsy, and 15 patients in combination cohorts evaluating SY-1365 in combination with carboplatin in patients with high-grade serous ovarian cancer and in combination with fulvestrant in patients with treatment-resistant metastatic HR+ breast cancer. We initiated the single-agent expansion cohorts at a dose of 80 mg/m^2 twice weekly and the combination cohorts at 53 mg/m^2 once weekly after having observed data from the dose-escalation portion of the trial demonstrating dose-dependent effects on CDK7 occupancy and downstream gene expression changes in blood cells as well as the confirmed partial response in a patient with recurrent clear cell ovarian cancer. During the expansion portion of the trial, adverse events occurring around the time of infusion of SY-1365, which we believe to be related to the intravenous administration of SY-1365, prompted us to evaluate lower doses of 53 mg/m^2 and 64 mg/m^2 in the single-agent cohorts and extended infusion times across all of the cohorts. Extended infusion times reduced peak drug concentrations while maintaining CDK7 target occupancy and appeared to reduce the overall frequency and severity of these peri-infusional adverse events, including headache, nausea and vomiting, supporting our belief that these adverse events were related to SY-1365 and not CDK7 inhibition generally. The best response observed across the expansion cohorts of the trial was stable disease, as defined by RECIST criteria. Of the 31 response-evaluable patients treated with SY-1365 as a single agent, 13 of them, or 42%, had stable disease. Of the 11 response-evaluable patients treated in the combination cohorts of the trial, seven of them, or 64%, had stable disease. Tumor biopsy data from the trial showed evidence of apoptosis in tumor tissue from patients treated at 80 mg/m^2, but not at lower doses. Based on preclinical and clinical data generated to date, we believe that sustaining the level of CDK7 target coverage needed to enhance clinical activity with SY-1365 would require more frequent dosing, or a higher dose that would necessitate lengthening the infusion time to manage tolerability. We believe that either approach could create an overly burdensome dosing regimen for patients that could be better addressed with an oral agent like SY-5609. This belief, coupled with the superior preclinical data generated with SY-5609 relative to SY-1365 and a competitive landscape in oncology increasingly focused on oral agents, led us to make a portfolio decision to discontinue further development of SY-1365 and prioritize the development of SY-5609.

SY-5609 Market Opportunity

With SY-5609, we believe that we have the opportunity to address significant unmet medical needs across a range of cancers. The initial disease-specific focus of our clinical development program for SY-5609 may include ovarian cancer, HR+ breast cancer, TNBC, colorectal cancer, and small cell lung cancer. We also believe there is an opportunity for SY-5609 in patients with solid tumors that have Rb pathway alterations.

Ovarian cancer is the fifth most common cause of cancer death in women. Currently, there are an estimated 63,000 ovarian cancer diagnoses each year in what we refer to as the developed pharmaceutical markets – the United States, Japan and the five largest European countries by population. Of these, approximately 70% have high-grade serous ovarian cancer and present with advanced disease at initial diagnosis.

Breast cancer is the most common tumor type in women and is the second leading cause of cancer death in women in the United States, after lung cancer. According to the American Cancer Society, approximately 276,000 new breast cancer cases will be diagnosed in the United States in 2020, with approximately 42,000 deaths from the disease. Breast cancer can be classified as HR+, human epidermal growth factor receptor 2, or HER2, positive, and TNBC (lacking estrogen, progesterone, and HER2 receptors). HR+/HER2- accounts for nearly 75% of breast cancer incidence, while HER2 (+/- HR) and TNBC account for 15% and 12% of cases, respectively. We anticipate focusing on the metastatic HR+/HER2-negative and TNBC patient populations with SY-5609. There are approximately 77,000 HR+/HER2-negative patients and 21,500 TNBC patients in the developed pharmaceutical markets.

Colorectal cancer is the third most commonly diagnosed cancer in men and women but is the second leading cause of death in the United States. The number of colorectal cancer cases in 2020 is estimated to be 500,000 across the developed pharmaceutical markets. In the United States. it is estimated that there will be 135,000 new cases, and approximately 55,000 metastatic stage patients, diagnosed this year. Chemotherapeutic regimens are the standard of care for initial treatment of metastatic colorectal cancer. Therapies targeted towards specific mutations such as BRAF or KRAS are currently being investigated in clinical trials.

Small cell lung cancer accounts for approximately 15% of all lung cancers but has an especially poor prognosis, with only 6% of patients surviving at five years following diagnosis. It is estimated that there will be approximately 63,000 new cases of small cell lung cancer diagnosed in the developed pharmaceutical markets in 2020. Small cell lung cancer can be classified as limited-stage disease (defined as Stages I, II, and III disease) and extensive-stage disease (Stage IV), with the latter accounting for approximately 70% of cases. The life expectancy of limited-stage small cell lung cancer is nearly two years, while life expectancy for patients with extensive-stage disease is less than one year.

Rb pathway alterations are present in a variety of solid tumors, including small cell lung cancer, pancreatic ductal adenocarcinoma, or PDAC, TNBC and high-grade serous ovarian cancer. It is believed that the loss of Rb function is obligatory in small cell lung cancer, while approximately one-third of PDAC and TNBC tumors and two-thirds of high-grade serous ovarian cancers are thought to have Rb pathway alterations. In addition, resistance to CDK4/6 inhibitors in HR+ breast cancer is associated with Rb loss.

Sickle Cell Disease

The first monogenic disease in which we focused our research efforts was sickle cell disease, where our objective is to provide a functional cure for patients by switching on the gamma-globin gene with an oral medicine. Using our gene control platform to elucidate mechanisms controlling gamma-globin gene expression, we have focused our efforts to date on components of LRF (leukemia/lymphoma-related factor) and the NuRD (nucleosome remodeling and histone deacetylation) complex as potential targets to switch on the gamma-globin gene, which is normally silenced a few months after birth. By turning on gamma-globin expression, we aim to induce the production of fetal hemoglobin, which is known to exert protective effects on the red blood cells of patients with sickle cell disease and beta thalassemia and to mitigate the clinical manifestations of those diseases.

At the American Society of Hematology Annual Meeting held in December 2019, or ASH 2019, we highlighted a portion of our sickle cell disease work by reporting that we had discovered and validated a novel fetal hemoglobin repressor, Nuclear Factor I X, or NFIX, that could serve as a potential target for therapeutic intervention. The preclinical data presented at ASH 2019 showed:

- increases in expression of gamma-globin mRNA comparable to known fetal hemoglobin repressors;
- detectable levels of fetal hemoglobin in nearly 100% of cells, compared to 16% of cells when the NFIX gene was not knocked down; and
- increases in total fetal hemoglobin levels to 40%, exceeding levels that are associated in the published literature with a functional cure in a subset of sickle cell patients.

In December 2019, we entered into a collaboration with GBT to discover, develop and commercialize novel therapies for sickle cell disease and beta thalassemia. See "—License and Collaboration Agreements–Global Blood Therapeutics" below.

Other Programs

We currently have several other programs in our preclinical and discovery pipeline, including a CDK12/13 inhibitor program, a program directed to inhibitors of a macrophage target in cancer and immune modulation, and discovery programs related to a gene control target to treat myotonic dystrophy type 1. We expect to nominate our next development candidate to enter IND-enabling preclinical studies by the end of 2021.

We are also using our platform to analyze gene expression programs in tumors and immune cells across various cancers and monogenic diseases to identify optimal points of therapeutic intervention in specific subsets of patients and to create a pipeline of novel product candidates targeting transcriptional and regulatory proteins. We are also using our platform in collaboration with third parties to identify and validate targets in diseases beyond our current areas of focus. To this end, we entered a target discovery, research collaboration and option agreement with Incyte in January 2018 under which we are using our platform to identify novel therapeutic targets with a focus on myeloproliferative neoplasms. See "—License and Collaboration Agreements–Incyte Corporation" below.

Intellectual Property

We file patent applications directed to various compositions of matter, formulations and methods related to our product candidates and compounds in earlier stages of development, methods related to our gene control platform, and other commercially relevant inventions. As of December 31, 2019, we own nine issued U.S. patents and 14 pending U.S. patent applications. We are pursuing or maintaining fifty corresponding patent applications that are pending or granted in various jurisdictions outside the United States, including Europe, Japan, Australia, Canada and China, and we own five applications that are pending in accordance with the Patent Cooperation Treaty, or PCT. In addition, as of December 31, 2019, we have field-limited exclusive licenses to six issued U.S. patents and nine corresponding applications that are pending or granted in various jurisdictions outside the United States, including Europe, Japan and Canada. A significant portion of the patents and applications we own or license pertain to our product candidates that are in clinical or pre-clinical development, to methods of using them in the treatment of disease, and to methods of selecting patients for treatment based on biomarker expression.

Our intellectual property portfolio as of December 31, 2019 is further described below. For some of our pending patent applications, prosecution has yet to commence. Prosecuting patent applications to allowance is often a lengthy process, during which the scope of the claims initially submitted for examination by various patent offices is often significantly narrowed, and some claims may never be granted. It is possible that we will amend the claims of our pending patent applications to limit their scope. We may also elect to abandon some of our pending patent applications, particularly those pending outside of the United States, if we determine these applications do not have strategic significance to our programs or platform.

SY-1425

The patent portfolio we own for SY-1425 contains four issued U.S. patents, two pending U.S. patent applications, and 21 applications pending or granted in countries other than the United States, including Europe, Japan, Australia, Canada and China. Generally, these patents and applications disclose methods of identifying and treating patients who are sensitive to RARα agonists, including SY-1425, based on the expression of certain biomarkers, including RARA and IRF8. The applications disclose methods of treating selected patients with SY-1425 alone or with a combination of SY-1425 and a second agent, such as azacitidine. One of our issued patents, U.S. Patent No. 9,845,508, covers methods of diagnosing and treating human patients suffering from non-APL AML by administering SY-1425; the patients are diagnosed based on the level of RARA messenger RNA, or mRNA, previously determined to be present in a sample of diseased cells from the subject. The granted claims of the second patent, U.S. Patent No. 10,167,518, cover methods of treating human subjects suffering from MDS. The diagnosis is again based on the level of RARA mRNA expression, and the subjects are treated with SY-1425. A third patent, U.S. Patent No. 9,868,994, covers methods of treating non-APL AML or MDS by administering SY-1425 to a patient when a defined sample obtained from the patient is determined to have an elevated level of IRF8 mRNA or elevated levels of both IRF8 and RARA mRNA. A fourth patent, U.S. Patent No. 10,240,210, covers methods of treating non-APL AML or MDS with a combination of SY-1425 (tamibarotene) and azacitidine when a defined sample from the subject has been determined to have an elevated RARA mRNA level or an elevated IRF8 mRNA level. We believe these four U.S. patents are eligible for listing in the FDA's "Orange Book." These patents, as well as any additional patents that may grant from applications claiming the benefit of the same filing date as the currently granted patents, have statutory expiration dates no earlier than March 2036. Patent term extensions could result in later expiration dates.

In addition, we have an exclusive license from TMRC to practice the inventions claimed in two U.S. patents and five corresponding patents granted in Canada and Europe. The claims of the U.S. patents are directed to a tamibarotene capsule preparation, to a crystal form of tamibarotene, medicaments comprising that form, and methods of making it. The U.S. patent covering capsule preparations has a statutory expiration date in April 2028, and the U.S. patent related to the crystalline form has a statutory expiration date in August 2021. We do not have composition of matter patent protection with respect to SY-1425.

SY-5609 and Other CDK7 Inhibitors

The patent portfolio we own for SY-5609 and our other CDK7 inhibitors, including SY-1365, contains patents and patent applications generally directed to the inhibitors, pharmaceutical formulations containing them, and methods of making and using them, including their use in treating various biomarker-selected patient populations. As of December 31, 2019, we own five issued U.S. patents, six pending U.S. patent applications, 22 corresponding applications pending or granted in countries outside the United States, including Europe, Japan, Australia, Canada and China, one provisional patent application, and four pending applications filed in accordance with the PCT. Any patent that has issued or will issue and that claims the benefit of the priority date of one or more of these patents or patent applications will have a statutory expiration date ranging from October 2034 to November 2039. Patent term adjustments or patent term extensions could result in later expiration dates.

Of the five issued U.S. patents that we own, U.S. Patent No. 10,106,526 covers compounds and pharmaceutical compositions generically describing SY-1365; U.S. Patent No. 10,059,690 specifically claims SY-1365 and pharmaceutical compositions containing SY-1365; U.S. Patent No. 10,519,135 covers pharmaceutical compositions containing stereoisomers of SY-1365; U.S. Patent No. 10,336,760 covers CDK7 inhibitors conforming to the structural formula provided; and U.S. Patent No. 10,308,648 covers CDK7 inhibitors conforming to the structural formula provided as well as pharmaceutically acceptable salts, solvates, hydrates, tautomers, and stereoisomers thereof. The first three of these patents have a statutory expiration date of April 2035, not including available patent term extensions. A patent covering SY-5609 and pharmaceutical compositions containing SY-5609, if granted, would have a statutory expiration date of November 2039, not including available patent term adjustments or patent term extensions.

Sickle Cell Disease

As of December 31, 2019, we own one U.S. provisional patent application directed to methods of treating hemoglobinopathies such as sickle cell disease.

Other Programs

The intellectual property portfolio that relates to programs other than those described above contains patents and patent applications directed to compositions of matter for inhibiting transcription factors and immuno-oncology targets in multiple compound families, and methods of treating various diseases, including cancer and immunological diseases, through inhibition of specific transcription factor(s) or gene products. As of December 31, 2019, we own five U.S. patent applications and one PCT application. Any U.S. or non-U.S. patents issuing from the pending applications or applications claiming priority to the pending applications covering transcription factor inhibitors, immuno-oncology target inhibitors or methods of treating disease by inhibition of transcription factors or gene products will have statutory expiration dates ranging from February 2031 to December 2038.

Platform

The patent portfolio directed to our platform includes patent applications and patents directed to super-enhancers and their detection and uses thereof to detect novel disease targets. As of December 31, 2019, we own one pending U.S. patent application and one pending patent application in Europe directed to these technologies which, if issued, will have a statutory expiration date of March 2034. In addition, we have an exclusive license to two issued U.S. patents (U.S. Patent Nos. 9,181,580 and 10,160,977) and one pending patent application in Europe for which we have received a Notice of Intention to Grant, directed to these technologies. The U.S. and foreign patent applications that we own are directed to the identification of new super-enhancer components and methods of treating diseases by targeting those novel components, and if issued, will have a statutory expiration date no earlier than March 2034. The licensed U.S. patents have a statutory expiration date of October 2033 and the licensed pending applications directed to super-enhancers and their detection and uses thereof to detect novel disease targets, if issued, will have a statutory expiration date no earlier than October 2033.

In most countries, including the United States, a patent expires 20 years from its earliest effective filing date. In the United States, a patent's term may be lengthened to compensate for delays by the U.S. Patent and Trademark Office, or USPTO, in examining and granting a patent or may be shortened if a patent is terminally disclaimed over an earlier filed patent. A patent that covers a therapeutic agent may also be eligible for patent term extension when FDA approval is granted, provided statutory and regulatory requirements are met. See "—Government Regulation and Product Approvals—Marketing Authorization" below for additional information on such exclusivity. If and when our products receive approval by the FDA or regulatory agencies in other countries, we expect to apply for a patent term extension on an issued patent covering a given product, depending upon the length of the clinical trials for each product 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 terms of any of our patents.

As with other biotechnology and pharmaceutical companies, our ability to exclude others from making, using, or selling our product candidates and other inventions will depend on our success in obtaining valid patent claims and enforcing those claims. One or more of our pending patent applications, and any that we may file or license from third parties in the future may not, however, proceed to grant as an issued patent. We also cannot predict the breadth of claims that may be allowed or enforced in our patents. Any patent 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, which is highly unpredictable. 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 limiting protection such patent would afford the respective product and any competitive advantage such patent may provide.

In addition to patents and pending patent applications, we rely upon unpatentable know-how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our proprietary information, in part, by executing non-competition, non-solicitation, confidentiality, and invention assignment agreements with our employees, collaborators, scientific advisors and consultants as appropriate. The confidentiality agreements we enter into are designed to protect our proprietary information and the agreements or clauses requiring assignment of inventions to us are designed to grant us ownership of technologies that are developed through our relationship with the respective counterparty. We cannot guarantee, however, that these agreements will afford us adequate protection of our intellectual property and proprietary information rights.

License and Collaboration Agreements

We are a party to collaborations in which we aim to use our platform to benefit patients with diseases beyond our current areas of focus, or that we believe will contribute to our ability to advance development and ultimately commercialize our product candidates. We expect to enter into additional collaborations in the future. For instance, we intend to seek to enter into collaborations where we believe that realizing the full commercial value of our development programs will require access to broader geographic markets or the pursuit of broader patient populations or indications. Our existing collaborations impose, and any collaborations we may enter into in the future are likely to impose, certain performance obligations on us.

In addition, we are a party to a number of license agreements under which we license patents, patent applications and other intellectual property from third parties. We enter into these agreements to augment our proprietary intellectual property portfolio. The licensed intellectual property covers some of the compounds that we are researching and developing and some of the scientific processes that we use. These licenses impose various diligence and financial payment obligations on us. We expect to continue to enter into these types of license agreements in the future.

Global Blood Therapeutics

In December 2019, we entered into a license and collaboration agreement with GBT with respect to a research collaboration to discover novel targets that induce fetal hemoglobin, in order to develop new small molecule treatments for sickle cell disease and beta thalassemia. Under the terms of the collaboration agreement, parties will use commercially reasonable efforts to identify at least one compound for the commencement of studies that are reasonably required to meet the requirements for filing an IND. Each party will be solely responsible for its own costs incurred to conduct its activities under the research plan, except that GBT will reimburse us for full-time employee and out-of-pocket costs and expenses that we incur in accordance with the agreed upon research budget. Unless earlier terminated or extended, the research program will end in December 2022. The term of the research program may be extended by one or two one-year extensions as mutually agreed upon.

Under the terms of the collaboration agreement, we granted to GBT an option to obtain an exclusive, worldwide license, with the right to sublicense, under relevant intellectual property rights and know-how of our company arising from the collaboration to develop, manufacture and commercialize any compounds or products resulting from the collaboration. GBT may exercise this option at any time during the period (i) commencing on the earlier of (a) the date of GBT's designation of the first IND candidate, or (b) if no IND candidate is so designated as of the expiration of the research term, the date of expiration of the research term, and (ii) ending on the 180th day after the date of expiration or earlier termination of the research term. GBT's exercise of the option will be subject to any required filings with the applicable antitrust authority as required by the antitrust laws and satisfaction of any applicable antitrust conditions.

After any exercise of the option, GBT will be solely responsible, at its own expense, for all development, manufacturing, regulatory activities and commercialization of licensed compounds and products worldwide. Under the collaboration agreement, GBT is required to use commercially reasonable efforts to develop (including to seek and obtain regulatory approval of) and, if regulatory approval is obtained, commercialize at least one product in any and all uses in the United States and any of the United Kingdom, Germany, France, Italy and Switzerland. In addition, we have an option to co-promote the first product in the United States.

GBT made an upfront payment of $20.0 million to us in January 2020. Should GBT exercise its license option, we could receive up to $315 million in option exercise, development, regulatory, commercialization and sales-based milestones per product candidate and product resulting from the collaboration. We are also entitled to receive, subject to certain reductions, tiered mid-to-high single digit royalties as percentages of calendar year net sales on any licensed product. GBT's obligation to pay royalties, on a licensed product-by-licensed product and country-by-country basis, will commence on the date of the first commercial sale of such licensed product in such country and end on the later of (a) the tenth anniversary of the first commercial sale of such licensed product in such country, (b) the expiration of the last to expire valid claim in our patent rights, the jointly-owned patent rights or certain other specified patent rights that cover such licensed product in such country, and (c) the expiration of regulatory exclusivity for such licensed product in such country.

Either party may terminate the collaboration agreement for the other party's uncured material breach or insolvency, and in certain other specified circumstances, subject to specified notice and cure periods. GBT may unilaterally terminate the collaboration agreement in its entirety, for any or no reason, upon nine-months' prior written notice to us if such notice is delivered during the research term, or 90 days' prior written notice to us if such notice is delivered after the expiration or termination of the research term. Upon the termination of the collaboration agreement in certain specified cases (including any unilateral termination by GBT), GBT has agreed to grant us, effective as of the effective date of such termination, a worldwide, exclusive, royalty-bearing license, with the right to grant sublicenses, under specified intellectual property necessary or useful for the development, manufacture or commercialization of licensed compounds and products for any and all uses, as well as engage in other customary technology transfer activities.

Incyte Corporation

In January 2018, we entered into a target discovery, research collaboration and option agreement with Incyte. Under this agreement, we will use our gene control platform to identify novel therapeutic targets with a focus on myeloproliferative neoplasms, and Incyte has received options to obtain exclusive worldwide rights to intellectual property resulting from the collaboration for the development and commercialization of therapeutic products directed to up to seven validated targets. For each option exercised by Incyte, Incyte will have the exclusive worldwide right to use the licensed intellectual property to develop and commercialize therapeutic products that modulate the target as to which the option was exercised.

Under the terms of the collaboration agreement, Incyte paid us $10.0 million in up-front consideration, consisting of $2.5 million in cash and $7.5 million in pre-paid research funding, or the pre-paid research amount. Our activities under this agreement are subject to a joint research plan and, subject to certain exceptions, Incyte is responsible for funding our activities under the research plan, including amounts in excess of the pre-paid research amount. Under the collaboration agreement, we are required to use commercially reasonable efforts to conduct the research services over a period commencing on the effective date of the collaboration agreement and ending upon the completion of specified target validation activities.

We are eligible to receive target selection milestone payments and option exercise fees of up to an aggregate of $54.0 million if Incyte selects the maximum number of targets for validation and exercises its options to obtain exclusive rights to collaboration intellectual property for therapeutic products directed to all seven validated targets. Should any therapeutic product be developed by Incyte against a target as to which Incyte has exercised its option to obtain exclusive rights to collaboration intellectual property, we will be eligible to receive milestone payments and, if approved and commercialized, royalty payments from Incyte. For each of the seven validated targets, we would become eligible to receive from Incyte a total of up to $50.0 million in development and regulatory milestone payments. If products arising from the collaboration are approved, we would become eligible to receive from Incyte, for each validated target, a total of up to $65.0 million in commercial milestone payments. Upon approval and commercialization of any therapeutic product resulting from the collaboration, we would become eligible to receive low single-digit royalties on net sales of such product.

The term of the collaboration agreement with Incyte will, unless terminated by a party early, expire when all royalty obligations for products arising from the collaboration expire. The agreement may be terminated by Incyte for convenience on sixty (60) days' prior written notice to us, or by us on thirty (30) days' written notice in the event Incyte or one of its affiliates or sublicensees challenges the validity or enforceability of certain patent rights controlled by us. The agreement may also be terminated by either of the parties on thirty (30) days' prior written notice in the event of an uncured material breach of the agreement by the other party or immediately in the case of certain bankruptcy events. If the collaboration agreement is terminated by Incyte for material breach, then we must refund any unexpended pre-paid research amount. Incyte's right to terminate for convenience and each party's right to terminate for uncured material breach may be exercised either with respect to the agreement in its entirety or, as applicable, in relation to the relevant validated target and associated therapeutic products.

In connection with the collaboration agreement, we sold 793,021 shares of our common stock to Incyte for an aggregate purchase price of $10.0 million in cash, or $12.61 per share, in a private placement. In addition, from the closing of this sale until the earlier of the second anniversary of such closing or the expiration or termination of the collaboration agreement, we have granted to Incyte the right to purchase up to its *pro rata* share of the securities offered in certain subsequent offerings of our common stock or common stock equivalents, subject to the terms and conditions set forth in the stock purchase agreement. In February 2018, we sold 144,505 additional shares of our common stock to Incyte at a price of $9.55 per share, resulting in proceeds to us of $1.4 million.

TMRC

In September 2015 we entered into, and in April 2016 we amended and restated, a license agreement with TMRC, which we refer to as the TMRC license agreement, pursuant to which TMRC granted us an exclusive license, with the right to sublicense, under TMRC patent rights, data, regulatory filings and other intellectual property for the North American and European development and commercialization of SY-1425 (tamibarotene) products for the treatment of human cancer indications. Under the TMRC license agreement, we have agreed to pay TMRC single-digit royalties based on net sales if TMRC's patents cover our product and low single-digit royalties based on net sales with respect to know-how licensed by TMRC during a predefined royalty term, and to make payments to TMRC upon meeting specified clinical and regulatory milestones in an aggregate amount of approximately $13.0 million per indication, of which $1.0 million was paid in the third quarter of 2016 upon successful dosing of the first patient in our Phase 2 clinical trial of SY-1425. Under the TMRC license agreement, we must use commercially reasonable efforts to, among other things, commence development activities within one year, to develop SY-1425 in at least one cancer indication, and, following marketing approval, to market the product. The license agreement expires on the expiration of the subject patent rights or 15 years after the date of first commercial sale of product, whichever is later. The TMRC license agreement may be terminated by either party if the other party is in breach and the breach is not cured within a required amount of time or if the other party is in bankruptcy. If we have reason to do so, we may also terminate the agreement after one year from the original effective date at our sole discretion.

In connection with the TMRC license agreement, in April 2016 we entered into a supply management agreement with TMRC. Pursuant to the supply management agreement, we and TMRC have agreed to establish a joint manufacturing committee to discuss strategy for supply of SY-1425. In addition, we have agreed to pay TMRC a fee for each kilogram of SY-1425 active pharmaceutical ingredient we procure for clinical trial or commercial use. The supply management agreement terminates on the expiration or termination of the TMRC license agreement, and our obligation to pay these fees survives the termination of the supply management agreement. In April 2016, we also entered into a standby license with TMRC and Toko Pharmaceuticals Ind. Co. Ltd., or Toko, the owner of the patent rights licensed to TMRC from which our license agreement with TMRC derives its rights, pursuant to which we obtain a standby license from Toko if Toko's license with TMRC is terminated.

Competition

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

We compete in the segments of the pharmaceutical, biotechnology and other related markets that address gene control and cancer. There are other companies working to develop therapies in the fields of gene control and cancer. These companies include divisions of large pharmaceutical companies and biotechnology companies of various sizes.

The most common methods of treating patients with cancer are surgery, radiation and drug therapy, including chemotherapy, hormone therapy and targeted drug therapy. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. While our product candidates may compete with many existing drug and other therapies, they may also be used in combination with or as an adjunct to these therapies. 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. As a result, the level of morbidity and mortality from cancer remains high.

In addition to currently marketed therapies, there are also a number of medicines in late stage clinical development to treat cancer. 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.

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

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

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

If the product candidates of our priority programs are approved for the indications for which we are currently planning clinical trials, they will compete with the drugs discussed below and will likely compete with other drugs currently in development.

SY-1425

We plan to initially develop SY-1425, our RARα agonist, for patients with AML. We intend to select patients for our clinical trials based on high-levels of RARα as measured by our proprietary RARA biomarker. We are aware of four new drugs approved by the FDA since 2018 for the treatment of AML or patient subsets within AML: ivosidenib, venetoclax, glasdegib and gilteritinib. SY-1425 may also face competition from other investigational products currently in clinical development for AML and MDS, including investigational products in late-stage development from Takeda Pharmaceutical Co. Ltd., Daiichi Sankyo Company, Limited, Agios Pharmaceuticals, Inc., Otsuka Pharmaceutical Co., Ltd., Roche Holding AG, Actinium Pharmaceuticals, Inc., GlycoMimetics, Inc., Arog Pharmaceuticals, Inc., Rafael Pharmaceuticals, Inc., MEI Pharma, Inc., argenx SE in collaboration with Janssen Pharmaceutica NV, Forty Seven, Inc., Aprea Therapeutics, Inc., SELLAS Life Sciences Group, Inc. and Bristol-Myers Squibb Co. We are not aware of any selective RARα agonist programs that are in active clinical development.

SY-5609

We are conducting a Phase 1 clinical trial of SY-5609 in patients with select advanced solid tumors. We are aware of selective CDK7 inhibitors being developed in early clinical trials by Carrick Therapeutics Ltd. and Eli Lilly & Co. and several other selective CDK7 inhibitor programs that we believe are in preclinical development, including programs from Aurigene Discovery Technologies Ltd. in collaboration with Exelixis, Inc., Ube Industries Ltd., Qurient Co. Ltd., and Yungjin Pharma Co., Ltd. SY-5609 may face competition from these CDK7 inhibitors.

Government Regulation and Product Approvals

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

Approval and Regulation of Drugs in the United States

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

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

- preclinical testing including laboratory tests, animal studies and formulation studies, which must be performed in accordance with the FDA's good laboratory practice, or GLP, regulations and standards;
- submission to the FDA of an IND for human clinical testing, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, representing each clinical site before each clinical trial may be initiated;
- performance of adequate and well-controlled human clinical trials to establish the safety, potency and purity of the product candidate for each proposed indication, in accordance with current good clinical practices, or GCP;
- preparation and submission to the FDA of a new drug application, or NDA, for a drug product which includes not only the results of the clinical trials, but also, detailed information on the chemistry, manufacture and quality controls for the product candidate and proposed labelling 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 an FDA inspection of the manufacturing facility or facilities, including those of third parties, at which the product candidate or components thereof are manufactured to assess compliance with current good manufacturing practices, or cGMP, requirements and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity;
- satisfactory completion of any FDA audits of the non-clinical and clinical trial sites to assure compliance with GCP and the integrity of clinical data in support of the NDA;

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

- compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and the potential requirement to conduct any post-approval studies required by the FDA.

Preclinical Studies

Before an applicant begins testing a product candidate with potential therapeutic value in humans, the product candidate enters the preclinical testing stage. Preclinical tests include laboratory evaluations of product chemistry, formulation and stability, as well as other studies to evaluate, among other things, the toxicity of the product candidate. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements, including GLP regulations and standards. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, and long-term toxicity studies, may continue after the IND is submitted.

The IND and IRB Processes

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

Following commencement of a clinical trial under an IND, the FDA may also place a clinical hold or partial clinical hold on that trial. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. For example, a specific protocol or part of a protocol is not allowed to proceed, while other protocols may do so. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical hold or partial clinical hold, an investigation may only resume after the FDA has notified the sponsor that the investigation may proceed. The FDA will base that determination on information provided by the sponsor correcting the deficiencies previously cited or otherwise satisfying the FDA that the investigation can proceed.

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

In addition to the foregoing IND requirements, an IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and reapprove the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. An IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product candidate has been associated with unexpected serious harm to patients.

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee, or DSMB. This group provides a recommendation as to whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the study. Suspension or termination of development during any phase of clinical trials can occur if it is determined that the participants or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by us based on evolving business objectives and/or competitive climate.

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

Expanded Access to an Investigational Drug for Treatment Use

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

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

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

In addition, on May 30, 2018, the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase I clinical trial and that 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 and dosage schedule. 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 status and a brief description of available results of the clinical trials must be submitted at least annually to the FDA. 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 completed 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.

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

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

The NDA is a vehicle through which applicants formally propose that the FDA approve a new product for marketing and sale in the United States for one or more indications. Every new drug product candidate must be the subject of an approved NDA before it may be commercialized in the United States. Under federal law, the submission of most NDAs is subject to an application user fee, which for federal fiscal year 2020 is $2,943,965 for an application requiring clinical data. The sponsor of an approved NDA is also subject to an annual program fee, which for fiscal year 2020 is $325,424. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for products with orphan designation and a waiver for certain small businesses.

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

Before approving an application, the FDA typically will inspect the facility or facilities where the product is or will be manufactured. These pre-approval inspections may cover all facilities associated with an NDA submission, including component manufacturing, finished product manufacturing and control testing laboratories. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. Under the FDA Reauthorization Act of 2017, the FDA must implement a protocol to expedite review of responses to inspection reports pertaining to certain applications, including applications for products in shortage or those for which approval is dependent on remediation of conditions identified in the inspection report.

In addition, as a condition of approval, the FDA may require an applicant to develop a REMS. REMS use risk minimization strategies beyond the professional labeling to ensure that the benefits of the product outweigh the potential risks. To determine whether a REMS is needed, the FDA will consider the size of the population likely to use the product, seriousness of the disease, expected benefit of the product, expected duration of treatment, seriousness of known or potential adverse events and whether the product is a new molecular entity.

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

Fast Track, Breakthrough Therapy and Priority Review

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, as applicable to our business, are referred to as fast track designation, breakthrough therapy designation and priority review 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.

Accelerated Approval Pathway

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

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints, but has indicated that such endpoints generally may support accelerated approval where the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate clinical benefit of a product.

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a product, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the development and approval of products for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit. Thus, the benefit of accelerated approval derives from the potential to receive approval based on surrogate endpoints sooner than possible for trials with clinical or survival endpoints, rather than deriving from any explicit shortening of the FDA approval timeline, as is the case with priority review.

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

The FDA's Decision on an NDA

On the basis of the FDA's evaluation of the application and accompanying information, including the results of the inspection of the manufacturing facilities, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA has committed to reviewing such resubmissions in two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

If the FDA approves a new product, it may limit the approved indications for use of the product. The agency may also require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including REMS, to help ensure that the benefits of the product outweigh the potential risks. REMS can include medication guides, communication plans for health care professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring and the use of patent registries. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Regulation

If regulatory approval for marketing of a product or new indication for an existing product is obtained, the sponsor will be required to comply with all regular post-approval regulatory requirements as well as any post-approval requirements that the FDA may have imposed as part of the approval process. The sponsor will be required to report, among other things, certain adverse reactions and manufacturing problems to the FDA, provide updated safety and efficacy information and comply with requirements concerning advertising and promotional labeling requirements. Manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMP regulations, which impose certain procedural and documentation requirements upon manufacturers. Accordingly, the sponsor and its third-party manufacturers must continue to expend time, money and effort in the areas of production and quality control to maintain compliance with cGMP regulations and other regulatory requirements.

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

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates the marketing, labeling, advertising and promotion of prescription drug products placed on the market. This regulation includes, among other things, standards and regulations for direct-to-consumer advertising, communications regarding unapproved uses, industry-sponsored scientific and educational activities, and promotional activities involving the Internet and social media. Promotional claims about a drug's safety or effectiveness are prohibited before the drug is approved. After approval, a drug product generally may not be promoted for uses that are not approved by the FDA, as reflected in the product's prescribing information. In the United States, health care professionals are generally permitted to prescribe drugs for such uses not described in the drug's labeling, known as off-label uses, because the FDA does not regulate the practice of medicine. However, FDA regulations impose rigorous restrictions on manufacturers' communications, prohibiting the promotion of off-label uses. It may be permissible, under very specific, narrow conditions, for a manufacturer to engage in nonpromotional, non-misleading communication regarding off-label information, such as distributing scientific or medical journal information.

If a company is found to have promoted off-label uses, it may become subject to adverse public relations and administrative and judicial enforcement by the FDA, the 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 DSCA, which regulate the distribution and tracing of prescription drug samples at the federal level, and set minimum standards for the regulation of distributors by the states. The PDMA, its implementing regulations and state laws limit the distribution of prescription pharmaceutical product samples, and the DSCA imposes requirements to ensure accountability in distribution and to identify and remove counterfeit and other illegitimate products from the market.

Pediatric Studies and Exclusivity

Under the Pediatric Research Equity Act of 2003, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. Sponsors must also submit pediatric study plans prior to the assessment data. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests and other information required by regulation. The applicant, the FDA, and the FDA's internal review committee must then review the information submitted, consult with each other and agree upon a final plan. The FDA or the applicant may request an amendment to the plan at any time.

For drugs intended to treat a serious or life-threatening disease or condition, the FDA must, upon the request of an applicant, meet to discuss preparation of the initial pediatric study plan or to discuss deferral or waiver of pediatric assessments. In addition, FDA will meet early in the development process to discuss pediatric study plans with sponsors and FDA must meet with sponsors by no later than the end-of-phase 1 meeting for serious or life-threatening diseases and by no later than ninety (90) days after 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. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

The FDA Reauthorization Act of 2017 established new requirements to govern certain molecularly targeted cancer indications. Any company that submits an NDA three years after the date of enactment of that statute must submit pediatric assessments with the NDA if the drug is intended for the treatment of an adult cancer and is directed at a molecular target that the FDA determines to be substantially relevant to the growth or progression of a pediatric cancer. The investigation must be designed to yield clinically meaningful pediatric study data regarding the dosing, safety and preliminary efficacy to inform pediatric labeling for the product.

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

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.

Section 505(b)(2) NDAs

NDAs for most new drug products are based on two full clinical studies that 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 product candidate for all or some of the label indications for which the referenced drug has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant.

Abbreviated New Drug Applications for Generic Drugs

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

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

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

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

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

Hatch-Waxman Patent Certification and the 30-Month Stay

Upon approval of an NDA or a supplement thereto, NDA sponsors are required to list with the FDA each patent with claims that cover the applicant's product or an approved method of using the product. Each of the patents listed by the NDA sponsor is published in the Orange Book. When an ANDA applicant files its application with the FDA, the applicant is required to certify to the FDA concerning any patents listed for the reference product in the Orange Book, except for patents covering methods of use for which the ANDA applicant is not seeking approval. To the extent that the Section 505(b)(2) applicant is relying on studies conducted for an already approved product, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book to the same extent that an ANDA applicant would.

Specifically, the applicant must certify with respect to each patent that:

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

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

If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days after the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months after the receipt of the Paragraph IV notice, expiration of the patent, or a decision in the infringement case that is favorable to the ANDA applicant.

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

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent restoration of up to five years for patent term lost during product development and the FDA regulatory review. The restoration period granted on a patent covering a product is typically one-half the time between the effective date of a clinical investigation involving human beings is begun and the submission date of an application, plus the time between the submission date of an application and the ultimate approval date. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date. Only one patent applicable to an approved product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent in question. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The United States Patent and Trademark Office 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, if the FDA determines that a companion diagnostic device is essential to the safe and effective use of a novel therapeutic product or indication, the FDA generally will not approve the therapeutic product or new therapeutic product indication if the companion diagnostic device is not approved or cleared for that indication. Approval or clearance of the companion diagnostic device will ensure that the device has been adequately evaluated and has adequate performance characteristics in the intended population. The review of *in vitro* companion diagnostics in conjunction with the review of our therapeutic treatments for cancer will, therefore, likely involve coordination of review by the FDA's Center for Drug Evaluation and Research and the FDA's Center for Devices and Radiological Health Office of In Vitro Diagnostics Device Evaluation and Safety.

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

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

PMA approval is not guaranteed, and the FDA may ultimately respond to a PMA submission with a not approvable determination based on deficiencies in the application and require additional clinical trial or other data that may be expensive and time-consuming to generate and that can substantially delay approval. If the FDA's evaluation of the PMA application is favorable, the FDA typically issues an approvable letter requiring the applicant's agreement to specific conditions, such as changes in labeling, or specific additional information, such as submission of final labeling, in order to secure final approval of the PMA. If the FDA's evaluation of the PMA or manufacturing facilities is not favorable, the FDA will deny approval of the PMA or issue a not approvable letter. A not approvable letter will outline the deficiencies in the application and, where practical, will identify what is necessary to make the PMA approvable. The FDA may also determine that additional clinical trials are necessary, in which case the PMA approval may be delayed for several months or years while the trials are conducted and then the data submitted in an amendment to the PMA. If the FDA concludes that the applicable criteria have been met, the FDA will issue a PMA for the approved indications, which can be more limited than those originally sought by the applicant. The PMA can include post-approval conditions that the FDA believes necessary to ensure the safety and effectiveness of the device, including, among other things, restrictions on labeling, promotion, sale and distribution. Once granted, PMA approval may be withdrawn by the FDA if compliance with post approval requirements, conditions of approval or other regulatory standards are not maintained or problems are identified following initial marketing.

After a device is placed on the market, it remains subject to significant regulatory requirements. Medical devices may be marketed only for the uses and indications for which they are cleared or approved. Device manufacturers must also establish registration and device listings with the FDA. A medical device manufacturer's manufacturing processes and those of its suppliers are required to comply with the applicable portions of the QSR, which cover the methods and documentation of the design, testing, production, processes, controls, quality assurance, labeling, packaging and shipping of medical devices. Domestic facility records and manufacturing processes are subject to periodic unscheduled inspections by the FDA. The FDA also may inspect foreign facilities that export products to the United States.

Healthcare 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 Healthcare Reform

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

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

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

There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and biologics and other medical products, government control and other changes to the health care system in the United States. In March 2010, the ACA was enacted, which includes measures that have significantly changed health care financing by both governmental and private insurers. The provisions of the ACA of importance to the pharmaceutical and biotechnology industry are, among others, the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drug agents or biologic agents, which is apportioned among these entities according to their market share in certain government health care programs;

- an increase in the rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13% of the average manufacturer price for branded and generic drugs, respectively;

- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% point-of-sale discounts to negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;

- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations, unless the drug is subject to discounts under the 340B drug discount program;

- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;

- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability;

- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;

- new requirements under the federal Physician Payments Sunshine Act for drug manufacturers to report information related to payments and other transfers of value made to physicians and teaching hospitals as well as ownership or investment interests held by physicians and their immediate family members;

- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;

- creation of the Independent Payment Advisory Board, which, if and when impaneled, will have authority to recommend certain changes to the Medicare program that could result in reduced payments for prescription drugs; and

- establishment of a Center for Medicare and Medicaid Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

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

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

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

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

Further, there have been several recent U.S. congressional inquiries and proposed federal and proposed and enacted state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products. At the federal level, Congress and the Trump Administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. For example, in May 2018, the Trump Administration issued a plan to lower drug prices. Under this blueprint for action, the Administration

indicated that the Department of Health and Human Services will: take steps to end the gaming of regulatory and patent processes by drug makers to unfairly protect monopolies; advance biosimilars and generics to boost price competition; evaluate the inclusion of prices in drug makers' ads to enhance price competition; speed access to and lower the cost of new drugs by clarifying policies for sharing information between insurers and drug makers; avoid excessive pricing by relying more on value-based pricing by expanding outcome-based payments in Medicare and Medicaid; work to give Part D plan sponsors more negotiation power with drug makers; examine which Medicare Part B drugs could be negotiated for a lower price by Part D plans, and improving the design of the Part B Competitive Acquisition Program; update Medicare's drug-pricing dashboard to increase transparency; prohibit Part D contracts that include "gag rules" that prevent pharmacists from informing patients when they could pay less out-of-pocket by not using insurance; and require that Part D plan members be provided with an annual statement of plan payments, out-of-pocket spending, and drug price increases. In addition, on December 23, 2019, the Trump Administration published a proposed rulemaking that, if finalized, would allow states or certain other non-federal government entities to submit importation program proposals to FDA for review and approval. Applicants would be required to demonstrate their importation plans pose no additional risk to public health and safety and will result in significant cost savings for consumers. At the same time, FDA issued draft guidance that would allow manufacturers to import their own FDA-approved drugs that are authorized for sale in other countries (multi-market approved products).

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

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 a marketing authorization application, or 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 new Clinical Trials Regulation, (EU) No 536/2014, or Clinical Trials Regulation, was adopted. The Regulation was published in June 2014 but is not expected to apply until later in 2020. The Clinical Trials Regulation will be directly applicable in all the EU Member States, repealing the current Clinical Trials Directive 2001/20/EC and replacing any national legislation that was put in place to implement the Directive. Conduct of all clinical trials performed in the EU will continue to be bound by currently applicable provisions until the new Clinical Trials Regulation becomes applicable. The extent to which on-going clinical trials will be governed by the Clinical Trials Regulation will depend on when the Clinical Trials 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 Trials Regulation becomes applicable the Clinical Trials Regulation will at that time begin to apply to the clinical trial.

The new Clinical Trials 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 (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 Trials Regulation.

PRIME Designation in the EU

In March 2016, the European Medicines Agency, or 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 may qualify for earlier entry into the PRIME scheme than larger companies. Many benefits accrue to sponsors of product candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other development program elements, and accelerated marketing authorization application assessment once a dossier has been submitted. Importantly, a dedicated Agency contact and rapporteur from the Committee for Human Medicinal Products, or CHMP, or Committee for Advanced Therapies are appointed early in 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 (i) a product-specific waiver, (ii) a class waiver or (iii) 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, 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 in particular 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. 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 efficacy and safety 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 may 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 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 marketing authorization application 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 a new chemical entity 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 tests, preclinical tests 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 further 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 n 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.

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 (i) 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 (ii) 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 ten 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 ten-year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if this product is safer, more effective or otherwise clinically superior to the original orphan medicinal product. The period of market exclusivity may, in addition, be reduced to six years if it can be demonstrated on the basis of available evidence that the original orphan medicinal product is sufficiently profitable not to justify maintenance of market exclusivity.

Regulatory Requirements after a Marketing Authorization has been Obtained

In case 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:

- Compliance with the EU's stringent pharmacovigilance or safety reporting rules must be ensured. These rules 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.

Brexit and the Regulatory Framework in the United Kingdom

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

Since the regulatory framework for pharmaceutical products in the United Kingdom covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from EU directives and regulations, Brexit could materially impact the future regulatory regime that applies to products and the approval of product candidates in the United Kingdom.

Pricing Decisions for Approved Products

In the EU, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies or so-called health technology assessments, in order to obtain reimbursement or pricing approval. For example, the EU provides options for its Member States to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. Member States may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other Member States allow companies to fix their own prices for products, but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the EU have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage health care expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the EU. The downward pressure on health care costs in general, particularly prescription products, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing 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 that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any products, if approved in those countries.

Sales and Marketing

We hold North American and European commercialization rights to SY-1425 for all cancer indications, and worldwide rights to SY-5609 and all of our other preclinical programs, other than our sickle cell disease program in which we are collaborating with GBT, for all potential indications. With respect to our sickle cell disease program, GBT has the option to obtain exclusive commercialization rights to products containing compounds arising out of the collaboration for all uses. If GBT exercises its option, we have a co-promotion right in the United States with respect to the first such product.

Subject to receiving marketing approval, we intend to build a focused sales and marketing organization in the United States and potentially in Europe to sell our products. We believe that such an organization will be able to address the community of physicians who are key specialists in treating the patient populations for which our product candidates are being developed. We also plan to build a marketing and sales management organization to create and implement marketing strategies for any products that we market through our own sales organization and to oversee and support our sales force. The responsibilities of the marketing organization would include developing educational initiatives with respect to approved products and establishing relationships with researchers and practitioners in relevant fields of medicine.

Outside of the United States and potentially Europe, where appropriate, we may elect in the future to utilize strategic partners, distributors or contract sales forces to assist in the commercialization of our products. In certain instances, we may consider building our own commercial infrastructure.

Manufacturing

We do not currently own or operate manufacturing facilities for the production of clinical or commercial quantities of our product candidates. Although we intend to rely on third-party contract manufacturers to produce our product candidates and any products we may develop in the future, we have recruited personnel with experience to manage these third-party contract manufacturers.

Employees

As of December 31, 2019, we had 83 full-time employees, including 37 employees with M.D., Ph.D. or Pharm.D. degrees. Of these full-time employees, 62 employees are engaged in research and development activities and 21 employees are engaged in general and administrative activities. None of our employees is represented by a labor union or covered by a collective bargaining agreement. We consider our relationship with our employees to be good.

Corporate Information

We were incorporated under the laws of the State of Delaware on November 9, 2011 under the name LS22, Inc. We changed our name to Syros Pharmaceuticals, Inc. on August 15, 2012. Our principal executive office is located at 35 CambridgePark Drive, 4th Floor, Cambridge, Massachusetts 02140, and our telephone number is (617) 744-1340.

Information Available on the Internet

Our Internet website address is *www.syros.com*. The information contained on, or that can be accessed through, our website is not a part of or incorporated by reference in this Annual Report on Form 10-K. We have included our website address in this in this Annual Report on Form 10-K solely as an inactive textual reference. We make available free of charge through our website our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Exchange Act. We make these reports available through the "SEC Filings" section of our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the SEC. We also make available, free of charge on our website, the reports filed with the U.S. Securities and Exchange Commission, or SEC, by our executive officers, directors and 10% stockholders pursuant to Section 16 under the Exchange Act as soon as reasonably practicable after copies of those filings are provided to us by those persons. You can review our electronically filed reports and other information that we file with the SEC on the SEC's website at *http://www.sec.gov*.

ITEM 1A. RISK FACTORS

We operate in a dynamic and rapidly changing business environment that involves multiple risks and substantial uncertainty. The following discussion addresses risks and uncertainties that could cause, or contribute to causing, actual results to differ from expectations in material ways. In evaluating our business, investors should pay particular attention to the risks and uncertainties described below and in other sections of this Annual Report on Form 10-K and in our subsequent filings with the SEC. These risks and uncertainties, or other events that we do not currently anticipate or that we currently deem immaterial also may affect our results of operations, cash flows and financial condition. The trading price of our common stock could also decline due to any of these risks, and you could lose all or part of your investment.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant losses since inception, expect to incur significant and increasing losses for at least the next several years, and may never achieve or maintain profitability.

We have incurred significant annual net operating losses in every year since our inception. We expect to continue to incur significant and increasing net operating losses for at least the next several years. Our net losses were $75.4 million, $62.3 million and $54.0 million for the years ended December 31, 2019, 2018 and 2017, respectively. As of December 31, 2019, we had an accumulated deficit of $293.0 million. We have not generated any revenues from product sales, have not completed the development of any product candidate and may never have a product candidate approved for commercialization. We have financed our operations to date primarily through the sale of equity securities. We have devoted substantially all of our financial resources and efforts to research and development and general and administrative expense to support such research and development. Our net losses may fluctuate significantly from quarter to quarter and year to year. Net losses and negative cash flows have had, and will continue to have, an adverse effect on our stockholders' equity and working capital.

We anticipate that our expenses will increase substantially if and as we:

- continue our planned clinical development activities with respect to SY-1425, a selective retinoic acid receptor alpha, or RARα, agonist that is currently being evaluated in combination with azacitidine, a hypomethylating agent, in a Phase 2 clinical trial, and SY-5609, an oral cyclin-dependent kinase 7, or CDK7, inhibitor that is in a Phase 1 clinical trial in patients with select advanced solid tumors;
- develop and seek approval of companion diagnostic tests for use in identifying patients who may benefit from treatment with our products and product candidates;
- initiate and continue research, preclinical and clinical development efforts for our research and preclinical programs;
- further develop our gene control platform;
- seek to identify and develop additional product candidates;
- acquire or in-license other product candidates or technologies;
- seek regulatory and marketing approvals for our product candidates that successfully complete clinical trials, if any;
- establish sales, marketing, distribution and other commercial infrastructure in the future to commercialize various products for which we may obtain marketing approval, if any;
- require the manufacture of larger quantities of product candidates for clinical development and, potentially, commercialization;
- maintain, expand and protect our intellectual property portfolio;
- hire and retain additional personnel and add operational, financial and management information systems, including personnel and systems to support our product development and commercialization efforts; and
- add equipment and physical infrastructure to support our research and development programs.

Our ability to become and remain profitable depends on our ability to generate revenue. We do not expect to generate significant revenue unless and until we are, or any future collaborator is, able to obtain marketing approval for, and successfully commercialize, one or more of our product candidates. Successful commercialization will require achievement of key milestones, including initiating and successfully completing clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those products for which we, or any of our future collaborators, may obtain marketing approval, satisfying any post-marketing requirements and obtaining reimbursement for our products from private insurance or government payors. Because of the uncertainties and risks associated with these activities, we are unable to accurately predict the timing and amount of revenues, and if or when we might achieve profitability. We and any future collaborators may never succeed in these activities and, even if we do, or any future collaborators do, we may never generate revenues that are large enough for us to achieve profitability. Even 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, expand our business, maintain our research and development efforts, diversify our pipeline of product candidates or continue our operations and cause a decline in the value of our common stock.

We have a limited operating history, no products approved for sale and no history of commercializing pharmaceutical products, which may make it difficult to evaluate the prospects for our future viability.

We commenced operations in 2011. Our operations to date have been limited to financing and staffing our company, building our research, development and operational capabilities, and conducting preclinical and early clinical research. We have not yet demonstrated an ability to advance a program into a pivotal clinical trial, obtain marketing approval for a product, manufacture a product at commercial scale or arrange for a third party to do so on our behalf, develop companion diagnostic tests or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Accordingly, you should consider our prospects in light of the costs, uncertainties, delays and difficulties frequently encountered by companies in the early stages of development, especially clinical stage biopharmaceutical companies such as ours. Any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successfully developing and commercializing pharmaceutical products.

We may encounter unforeseen expenses, difficulties, complications, delays and other known or unknown factors in achieving our business objectives. We will eventually need to transition from a company with a development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

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

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

Developing pharmaceutical products, including conducting preclinical studies and clinical trials, is a very time consuming, expensive and uncertain process that takes years to complete. We expect our expenses to increase in connection with our ongoing activities, particularly with respect to our ongoing Phase 2 clinical trial of SY-1425 in combination with azacitidine and the development of a companion diagnostic test for use in identifying patients who may benefit from treatment with SY-1425, and our Phase 1 clinical trial of SY-5609 in patients with select advanced solid tumors, and as we advance our existing research and preclinical pipeline, initiate new research, preclinical and clinical development efforts, and seek marketing approval for any product candidates and companion diagnostic tests that we or a vendor successfully develop. Moreover, under license agreements with various licensors, we are obligated to make milestone payments upon the successful completion of specified development and commercialization activities for products or product candidates covered by licensed intellectual property rights. In addition, if we obtain marketing approval for any product candidate that we may successfully develop, we may 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 a future collaborator. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we may be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

We will be required to expend significant funds in order to advance the development of SY-1425 and SY-5609, as well as our other research and preclinical programs. In addition, while we may seek one or more collaborators for future development of our current product candidates or any future product candidates that we may develop for one or more indications, we may not be able to enter into a collaboration for any of our product candidates for such indications on suitable terms, on a timely basis, or at all. In any event, our existing cash, cash equivalents and marketable securities will not be sufficient to fund all of the efforts that we plan to undertake or to fund the completion of development of our product candidates or our other preclinical programs. Accordingly, we will be required to obtain further funding through public or private equity offerings, debt financings, collaborations and licensing arrangements or other sources. We do not have any committed external source of funds to support our internal research and development efforts. Adequate additional financing may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy.

We believe that our cash, cash equivalents and marketable securities as of December 31, 2019, together with the $20.0 million up-front license fee received from Global Blood Therapeutics, Inc., or GBT, in January 2020 in connection with entry into our sickle cell disease collaboration in December 2019 and the $20.0 million drawn down on the term loan obtained from Oxford Finance LLC, or Oxford, in February 2020, will enable us to fund our planned operating expense and capital expenditure requirements into 2022. Our estimate as to how long we expect our existing cash, cash equivalents, and marketable securities to be able to continue 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 funding requirements, both short-term and long-term, will depend on many factors, including:

- the scope, progress, timing, costs and results of clinical trials of SY-1425 and SY-5609 and any associated companion diagnostic tests;
- the timing of wind-down activities for SY-1365 following our announcement in October 2019 that we are ceasing further development of that product candidate as part of a prioritization of our CDK7 product portfolio;
- research and preclinical development efforts for any future product candidates that we may develop;
- the number of future product candidates that we pursue and their development requirements;
- our ability to enter into, and the terms and timing of, any collaborations, licensing agreements or other arrangements;
- whether a drug candidate will be nominated to enter investigational new drug application-enabling studies under our sickle cell disease collaboration with GBT, whether GBT will exercise its option to exclusively license intellectual property arising from the collaboration, whether and when any option exercise fees, milestone payments or royalties under the collaboration agreement with GBT will ever be paid, and whether we exercise our U.S. co-promotion option under the GBT agreement;
- whether our target discovery collaboration with Incyte Corporation, or Incyte, will yield any validated targets, whether Incyte will exercise any of its options to exclusively license intellectual property directed to such targets, and whether and when any of the target validation fees, option exercise fees, milestone payments or royalties under the collaboration agreement with Incyte will ever be paid;
- the outcome, timing and costs of seeking regulatory approvals;
- the costs of commercialization activities for any of our product candidates that receive marketing approval to the extent such costs are not the responsibility of any future collaborators, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities;
- the costs of acquiring potential new product candidates or technology;
- the costs of any physician education programs relating to selecting and treating genomically defined patient populations;

- the timing and amount of milestone and other payments due to licensors for patent and technology rights used in our gene control platform or to TMRC Co. Ltd., or TMRC, associated with the development, manufacture and commercialization of SY-1425;

- revenue received from commercial sales, if any, of our current and future product candidates;

- our headcount growth and associated costs as we advance our research and development programs and establish a commercial infrastructure; and

- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights and defending against intellectual property related claims.

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

We expect our expenses to increase in connection with our planned operations. To the extent that we raise additional capital through the sale of common stock, convertible securities or other equity securities, as we did through concurrent public offerings of our equity securities in April 2019, the ownership interests of our existing stockholders may be diluted, and the terms of these securities could include liquidation or other preferences and anti-dilution protections that could adversely affect our stockholders' rights. In addition, debt financing, such as our term loan facility with Oxford that we entered in February 2020, has created fixed payment obligations and imposed restrictive covenants that limit our ability to take specific actions, such as incurring additional debt, making capital expenditures, creating liens, redeeming stock or declaring dividends, that could adversely impact our ability to conduct our business. 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 additional funds through collaborations or marketing, distribution or licensing arrangements with third parties, such as our collaboration agreement with GBT, we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

The terms of our Loan and Security Agreement place restrictions on our operating and financial flexibility.

In February 2020, we entered into a Loan and Security Agreement with Oxford, which is secured by substantially all of our currently owned or later acquired personal property other than our intellectual property (but including the right to payments and proceeds of intellectual property), which is subject to a negative pledge. We refer to the Loan and Security Agreement with Oxford as the Loan Agreement. We borrowed $20.0 million upon execution of the Loan Agreement. Two additional term loan advances of $20.0 million each will be available under the Loan Agreement, subject to certain terms and conditions, including the achievement of certain milestones.

The Loan Agreement contains representations and warranties, affirmative and negative covenants applicable to us and our subsidiaries and events of default, as more fully described in the Loan Agreement. The affirmative covenants include, among others, covenants requiring us and our subsidiaries to maintain our legal existence, good standing and material governmental approvals, deliver certain financial reports, maintain insurance coverage and maintain certain cash balances in controlled accounts. The negative covenants include, among others, restrictions on dispositions, changes in business, management, ownership or business locations, mergers or acquisitions, indebtedness, encumbrances, maintenance of collateral accounts, distributions, investments, transactions with affiliates and subordinated debt.

The Loan Agreement also includes events of default, the occurrence and during the continuation of which provide Oxford, as collateral agent, with the right to exercise remedies against us and the collateral securing the loans under the Loan Agreement, including foreclosure against our property securing the Loan Agreement, including our cash, potentially requiring us to renegotiate our agreement on terms less favorable to us, or to immediately cease operations. These events of default include, among other things, the nonpayment of principal or interest, violations of covenants, material adverse changes, attachment, levy, restraint on business, cross-defaults on material indebtedness, insolvency, material judgments, misrepresentations, subordinated debt, governmental approvals, lien priority and delisting.

Further, if we are liquidated, the Lenders' right to repayment would be senior to the rights of the holders of our common stock to receive any proceeds from the liquidation. Oxford could declare a default upon the occurrence of any event that they interpret as a material adverse change as defined under the Loan Agreement, thereby requiring us to repay the loan immediately or to attempt to reverse the declaration of default through negotiation or litigation. Any declaration by Oxford of an event of default could significantly harm our business and prospects and could cause the price of our common stock to decline.

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

Our approach to the discovery and development of product candidates based on our gene control platform is novel and unproven, and we do not know whether we will be able to develop any products of commercial value.

We are focused on discovering and developing medicines for the treatment of cancer and other diseases based upon our gene control platform. We are leveraging our platform to create a pipeline of gene control product candidates for genomically defined patients whose diseases have not been adequately addressed to date by other genomics approaches and to design and conduct efficient clinical trials with a higher likelihood of success. While we believe that applying our gene control platform to create medicines for genomically defined patient populations may potentially enable drug research and clinical development that is more efficient than conventional small molecule drug research and development, our approach is both novel and unproven. Because our approach is both novel and unproven, the cost and time needed to develop our product candidates is difficult to predict, and our efforts may not result in the discovery and development of commercially viable medicines. We may also be incorrect about the effects of our product candidates on the diseases of genomically defined patient populations, which may limit the utility of our approach or the perception of the utility of our approach. Furthermore, our estimates of genomically defined patient populations available for study and treatment may be lower than expected, which could adversely affect our ability to conduct clinical trials and may also adversely affect the size of any market for medicines we may successfully commercialize.

We have not yet succeeded and may never succeed in demonstrating efficacy and safety for our current or any future product candidates in a pivotal clinical trial or in obtaining marketing approval thereafter. For example, although we have discovered and evaluated compounds using our novel gene control platform, we have not yet demonstrated sufficient safety or efficacy of any of our product candidates in clinical trials to warrant pivotal clinical development in the patient population studied.

Our gene control platform may fail to help us discover and develop additional potential product candidates.

A significant portion of the research that we are conducting involves identifying novel targets and points of intervention and developing new compounds using our gene control platform. The drug discovery that we are conducting using our gene control platform may not be successful in identifying compounds that have commercial value or therapeutic utility. Our gene control platform may initially show promise in identifying potential product candidates, yet fail to yield viable product candidates for clinical development or commercialization for a number of reasons, including:

- insights regarding disease targets that are obtained through the use of our gene control platform may be generated independently through alternative approaches or be published by third parties;
- compounds created through our gene control platform may not demonstrate efficacy, safety or tolerability;
- potential product candidates may, on further study, be shown to have harmful side effects or other characteristics that indicate that they are unlikely to receive marketing approval and achieve market acceptance;
- competitors may develop alternative therapies that render our potential product candidates non-competitive or less attractive; or
- a potential product candidate may not be capable of being produced at an acceptable cost.

Our research programs to identify new product candidates will require substantial technical, financial and human resources, and we may be unsuccessful in our efforts to identify new product candidates. If we are unable to identify suitable additional compounds for preclinical and clinical development, our ability to develop product candidates and obtain product revenues in future periods could be compromised, which could result in significant harm to our financial position and adversely impact our stock price.

In the near term, we are dependent on the success of SY-1425 and SY-5609. If we are unable to initiate or complete the clinical development of, obtain marketing approval for or successfully commercialize SY-1425 or SY-5609, either alone or with a collaborator, or if we experience significant delays in doing so, our business could be substantially harmed.

We currently have no products approved for sale and are investing a significant portion of our efforts and financial resources in the development of SY-1425 and SY-5609. Our prospects are substantially dependent on our ability, or that of any future collaborator, to develop, obtain marketing approval for and successfully commercialize product candidates in one or more disease indications.

The success of SY-1425 and SY-5609 will depend on several factors, including the following:

- successful initiation, enrollment and completion of clinical trials;
- a safety, tolerability and efficacy profile, alone or in combination with other approved or investigational products, that is satisfactory to the U.S. Food and Drug Administration, or FDA, or any comparable foreign regulatory authority for marketing approval;
- timely receipt of marketing approvals from applicable regulatory authorities;
- the successful development and approval of companion diagnostic tests for use in identifying patients who may benefit from treatment with SY-1425;
- competition from approved or other investigational agents or changes in the standard of care for the disease indications we are pursuing;
- the performance of our future collaborators, if any;
- the extent of any required post-marketing approval commitments to applicable regulatory authorities;
- establishment of supply arrangements with third-party suppliers of raw materials and drug substance and drug product manufacturers;
- establishment of arrangements with third-party manufacturers to obtain finished drug product that is appropriately packaged for sale;
- adequate ongoing availability of raw materials and drug product for clinical development and any commercial sales;
- obtaining and maintaining patent, trade secret protection and regulatory exclusivity, both in the United States and internationally, including our ability to maintain our license agreement with TMRC;
- protection of our rights in our intellectual property portfolio;
- successful launch of commercial sales following any marketing approval;
- a continued acceptable safety profile following any marketing approval;
- commercial acceptance by patients, the medical community and third-party payors;
- successful identification of biomarkers for patient selection; and
- our ability to compete with other therapies.

Many of these factors are beyond our control, including clinical development, the regulatory submission process, potential threats to our intellectual property rights and the manufacturing, marketing and sales efforts of any future collaborator. If we are unable to develop, receive marketing approval for and successfully commercialize SY-1425 or SY-5609, on our own or with any future collaborator, or experience delays as a result of any of these factors or otherwise, our business could be substantially harmed.

If clinical trials of any product candidates that we, or any future collaborators, may develop fail to satisfactorily demonstrate safety and efficacy to the FDA and other regulators, we, or any future collaborators, may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development and commercialization of these product candidates.

We, and any future collaborators, are not permitted to commercialize, market, promote or sell any product candidate in the United States without obtaining marketing approval from the FDA. Foreign regulatory authorities, such as the European Medicines Agency, or the EMA, impose similar requirements. We, and any future collaborators, must complete extensive preclinical development and clinical trials to demonstrate the safety and efficacy of our product candidates in humans before we will be able to obtain these approvals.

We are conducting a Phase 2 clinical trial of SY-1425 in combination with azacitidine in genomically defined subsets of patients with acute myeloid leukemia, or AML, who are identified using our RARA biomarker. We anticipate reporting potential proof-of-concept data in the fourth quarter of 2020 from a trial cohort in patients with RARA-positive relapsed or refractory AML, and mature data in the fourth quarter of 2020 from trial cohorts in patients with newly diagnosed AML who are not suitable candidates for standard chemotherapy. We initiated a Phase 1 clinical trial of SY-5609 in the first quarter of 2020 in patients with select solid tumors. We expect to report initial safety, tolerability, pharmacokinetic and pharmacodynamic data from the dose escalation portion of the trial in the fourth quarter of 2020 as well as additional dose escalation data, including clinical activity data, in mid-2021. Our anticipated time to data in our clinical trials and the quantity of data to be presented from these trials is and will continue to be subject to our continued ability to recruit eligible patients and the satisfaction by patients of other eligibility criteria for participation in the trial. In the case of SY-1425, our time to data is also dependent on the prevalence of patients with the RARA biomarker, and the impact of new product approvals in the AML field. The rate of patient enrollment in the trial is difficult to predict. As a result, there can be no assurance that we will enroll or have data from the trial when we anticipate.

Clinical testing is expensive, is difficult to design and implement, can take many years to complete and is inherently uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. The clinical development of our product candidates is susceptible to the risk of failure inherent at any stage of product development, including failure to demonstrate efficacy in a clinical trial or across a broad population of patients, the occurrence of adverse events that are severe or medically or commercially unacceptable, failure to comply with protocols or applicable regulatory requirements and determination by the FDA or any comparable foreign regulatory authority that a product candidate may not continue development or is not approvable. It is also 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. For example, in December 2017 we reported data from our Phase 2 clinical trial evaluating SY-1425 as a single agent in genomically defined subsets of patients with relapsed or refractory AML and higher risk myelodysplastic syndrome, or MDS. While biological and clinical activity was observed in certain patients enrolled in the trial, the data were not sufficiently robust to warrant further development of SY-1425 as a single agent in these patient populations and we elected to cease further development in the portions of our Phase 2 clinical trial evaluating SY-1425 as a single agent. We face a similar risk of failure in our ongoing evaluation of SY-1425 in combination with azacitidine. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any. Similarly, in our clinical trials we may fail to detect toxicity or intolerability caused by our product candidates, or mistakenly believe that our product candidates are toxic or not well tolerated when that is not in fact the case.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us, or any future collaborators, and impair our ability to generate revenues from product sales, regulatory and commercialization milestones and royalties. Moreover, if we, or any future collaborators, are required to conduct additional clinical trials or other testing of our product candidates beyond the trials and testing that we or they contemplate, if we, or they, are unable to successfully complete clinical trials of our product candidates or other testing, or the results of these trials or tests are unfavorable, uncertain or are only modestly favorable, or there are unacceptable safety concerns associated with our product candidates, we, or any future collaborators, may:

- incur additional unplanned costs;
- be delayed in obtaining marketing approval for our product candidates;
- not obtain marketing approval at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;

- obtain approval with labeling that includes significant use or distribution restrictions or significant safety warnings, including boxed warnings;

- be subject to additional post-marketing testing or other requirements; or

- be required to remove the product from the market after obtaining marketing approval.

Our failure to successfully initiate 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 would significantly harm our business.

Adverse events or undesirable side effects caused by, or other unexpected properties of, product candidates that we develop may be identified during development and could delay or prevent their marketing approval or limit their use.

Adverse events or undesirable side effects caused by, or other unexpected properties of, SY-1425, SY-5609 or any future product candidates that we may develop could cause us, any future collaborators, an institutional review board or regulatory authorities to interrupt, delay or halt clinical trials of one or more of our product candidates and could result in a more restrictive label or the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities. Because gene control techniques are relatively new, side effects from gene control approaches may be unpredictable. Tamibarotene, the active ingredient in SY-1425, has been observed to be associated with adverse events, such as mild or moderate dry skin, skin rash, headache and bone pain, as well as retinoic acid syndrome and elevated levels of cholesterol, lipids, liver function enzymes and white blood cells, which were severe in certain cases. Furthermore, retinoids such as SY-1425 may cause birth defects and therefore may carry a warning on their label. Other examples of retinoids, a class of chemical compounds that are related to vitamin A, include all trans retinoic acid (also known as ATRA), Retin-A, retinol (found in over-the-counter skin creams), isotretinoin and bexarotene. In addition, we have extremely limited experience administering SY-5609 to humans, so the safety profile that SY-5609 will demonstrate in human clinical trials remains uncertain. Adverse events reported with non-selective cyclin dependent kinase, or CDK, inhibitors include myelosuppression. Adverse events related to SY-1365, an intravenously, or IV, administered CDK7 inhibitor included headache, nausea and vomiting, and the dose-limiting toxicities observed in our Phase 1 clinical trial of SY-1365 included headache, coronary vasospasm and fatigue. While SY-5609 is a selective inhibitor of CDK7 that is administered orally, we cannot guarantee that, in the clinical development of SY-5609, we will not observe similar or more severe adverse events than those observed with these other CDK inhibitors.

We also are evaluating the administration of tamibarotene in combination with azacitidine in patients with AML, and we may evaluate SY-5609 in combination with other therapeutic agents following completion of the dose escalation phase of our planned Phase 1 clinical trial. We cannot predict at this time whether the combination of our product candidates with another product, or with any premedication administered to mitigate potential side effects, will be well tolerated by patients in clinical studies or that any unexpected adverse events or undesirable side effects will not occur. If any of our product candidates is associated with adverse events or undesirable side effects or has properties that are unexpected, we, or any future collaborators, may need to abandon development or limit development of that product candidate to certain uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. Many compounds that initially showed promise in clinical or earlier stage testing have later been found to cause undesirable or unexpected side effects that prevented further development of the compound.

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

We, or any future collaborators, may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent clinical development, marketing approval or commercialization of our current product candidates or any future product candidates that we, or any future collaborators, may develop, including:

- regulators or institutional review boards may not authorize us, any future collaborators or our or their investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;

- we, or any future collaborators, may experience delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;

- clinical trials of our product candidates may produce unfavorable or inconclusive results;
- we, or any future collaborators, may decide, or regulators may require us or them, to conduct additional clinical trials or abandon product development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we, or any future collaborators, anticipate, patient enrollment in these clinical trials may be slower than we, or any future collaborators, anticipate or participants may drop out of these clinical trials at a higher rate than we, or any future collaborators, anticipate;
- our estimates of the genomically defined patient populations available for study may be higher than actual patient numbers and result in our inability to sufficiently enroll our trials;
- the cost of planned clinical trials of our product candidates may be greater than we anticipate;
- our third-party contractors or those of any future collaborators, including those manufacturing our product candidates or components or ingredients thereof or conducting clinical trials on our behalf or on behalf of any future collaborators, may fail to comply with regulatory requirements or meet their contractual obligations to us or any future collaborators in a timely manner or at all;
- patients that enroll in a clinical trial may misrepresent their eligibility to do so or may otherwise not comply with the clinical trial protocol, resulting in the need to drop the patients from the clinical trial, increase the needed enrollment size for the clinical trial or extend the clinical trial's duration;
- we, or any future collaborators, may have to delay, suspend or terminate clinical trials of our product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of the product candidate;
- regulators or institutional review boards may require that we, or any future collaborators, or our or their investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or their standards of conduct, a finding that the participants are being exposed to unacceptable health risks, undesirable side effects or other unexpected characteristics of the product candidate or findings of undesirable effects caused by a chemically or mechanistically similar product or product candidate;
- the FDA or comparable foreign regulatory authorities may disagree with our, or any future collaborators', clinical trial designs or our or their interpretation of data from preclinical studies and clinical trials;
- the FDA or comparable foreign regulatory authorities may fail to approve or subsequently find fault with the manufacturing processes or facilities of third-party manufacturers with which we, or any future collaborators, enter into agreements for clinical and commercial supplies;
- the supply or quality of raw materials or manufactured product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient, inadequate or not available at an acceptable cost, or we may experience interruptions in supply; and
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient to obtain marketing approval.

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

Failure to successfully validate, develop and obtain regulatory approval for companion diagnostics could harm our drug development strategy.

As one of the key elements of our development strategy, we seek to identify genomically defined subsets of patients within a disease category who may derive benefit from the product candidates we are developing. In collaboration with partners, we plan to develop companion diagnostics to help us to more accurately identify patients within a particular subset, both during our clinical trials and in connection with the commercialization of our product candidates that we are developing or may in the future develop. Companion diagnostics are subject to regulation by the FDA and comparable foreign regulatory authorities as medical devices and require separate regulatory approval prior to commercialization. We do not develop companion diagnostics internally and thus we will be dependent on the sustained cooperation and effort of one or more third-party collaborators in developing, obtaining approval for, and commercializing these companion diagnostics. We and our collaborators may encounter difficulties in developing and obtaining approval for the companion diagnostics, including issues relating to selectivity/specificity, analytical validation, reproducibility, or clinical validation. Any delay or failure by our collaborators to develop or obtain regulatory approval of the companion diagnostics could delay or prevent approval of our product candidates. In addition, our collaborators may encounter production difficulties that could constrain the supply of the companion diagnostics, and both they and we may have difficulties gaining acceptance of the use of the companion diagnostics in the clinical community. If such companion diagnostics fail to gain market acceptance, it would have an adverse effect on our ability to derive revenues from sales, if any, of our products. In addition, any companion diagnostic collaborator with whom we contract may decide not to commercialize or to discontinue selling or manufacturing the companion diagnostic that we anticipate using in connection with development and commercialization of our product candidates, or our relationship with such collaborator may otherwise terminate. We may not be able to enter into arrangements with another provider to obtain supplies of an alternative diagnostic test for use in connection with the development and commercialization of our product candidates or do so on commercially reasonable terms, which could adversely affect and/or delay the development or commercialization of our product candidates.

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

We, or any future collaborators, may not be able to initiate or continue clinical trials for our current product candidates or any future product candidates that we, or any future collaborators, may develop if we, or they, are unable to locate and enroll a sufficient number of eligible patients to participate in clinical trials. Patient enrollment is a significant factor in the timing of clinical trials, and is affected by many factors, including:

- the size and nature of the patient population;
- the severity of the disease under investigation;
- the availability of approved or investigational therapeutics for the relevant disease;
- the proximity of patients to clinical sites;
- the eligibility criteria for the trial;
- the design of the clinical trial;
- efforts to facilitate timely enrollment;
- competing clinical trials;
- clinicians' and patients' perceptions as to the potential advantages and risks of the drug being studied in relation to other available therapies, including any new drugs that may be approved for the indications we are investigating; and
- actual or threatened public health emergencies and outbreaks of disease (including, for example, the recent coronavirus outbreak.
- actual or threatened public health emergencies and outbreaks of disease (including, for example, the recent coronavirus outbreak.

In particular, we intend to enrich our clinical trials with patients most likely to respond to our gene control therapies. Genomically defined diseases may, however, have relatively low prevalence and it may be difficult for us or third parties with whom we collaborate to identify patients for our trials, which may lead to delays in enrollment for our trials. We intend to develop, or engage third parties to develop, companion diagnostics for use in our clinical trials, but we or such third parties may not be successful in developing such companion diagnostics, furthering the difficulty in identifying genomically defined subsets of patients for our clinical trials. Moreover, in light of the recent approval of new products for the treatment of AML, there is substantial competition for patients to be enrolled in clinical trials for this disease. Our inability, or the inability of any future collaborators, to enroll a sufficient number of patients for our, or their, clinical trials could result in significant delays or may require us or them to abandon one or more clinical trials altogether. Enrollment delays in our, or their, clinical trials may result in increased development costs for our product candidates, delay or halt the development of and approval processes for our product candidates and jeopardize our, or any future collaborators', ability to commence sales of and generate revenues from our product candidates, which could cause the value of our company to decline and limit our ability to obtain additional financing, if needed.

Results of preclinical studies and early clinical trials may not be predictive of results of future or late-stage clinical trials.

The data supporting our clinical development strategies for SY-1425 and SY-5609 have been derived entirely from preclinical studies and, in the case of SY-1425, early clinical trials. We cannot assure you that we will be able to replicate in human clinical trials the results we observed in earlier studies. Moreover, the outcome of preclinical studies and early clinical trials may not be predictive of the success of later or late-stage 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 early clinical trials have nonetheless failed to successfully complete later or late-stage clinical trials of, or obtain marketing approval for, the product candidates. Even if we, or any future collaborators, believe that the results of clinical trials for our product candidates warrant marketing approval, the FDA or comparable foreign regulatory authorities may disagree and may not grant marketing approval of our product candidates.

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

We have never obtained marketing approval for a product candidate and we may be unable to obtain, or may be delayed in obtaining, marketing approval for our current product candidates or any future product candidates that we, or any future collaborators, may develop.

We have never obtained marketing approval for a product candidate. It is possible that the FDA may refuse to accept for substantive review any new drug applications, or NDAs, that we submit for our product candidates or may conclude after review of our data that our application is insufficient to obtain marketing approval of our product candidates. If the FDA does not accept or approve our NDAs for any of our product candidates, it may require that we conduct additional clinical trials, preclinical studies or manufacturing validation studies and submit that data before it will reconsider our applications. Depending on the extent of these or any other FDA-required trials or studies, approval of any NDA or application that we submit may be delayed by several years, or may require us to expend more resources than we have available. It is also possible that additional trials or studies, if performed and completed, may not be considered sufficient by the FDA to approve our NDAs. In addition, our development programs contemplate the development of companion diagnostics by our third-party collaborators. Companion diagnostics are subject to regulation as medical devices and must themselves be approved for marketing by the FDA or certain other foreign regulatory agencies before we may commercialize our product candidates.

Any delay in obtaining, or an inability to obtain, marketing approvals would prevent us from commercializing our product candidates or any companion diagnostics, generating revenues and achieving and sustaining profitability. If any of these outcomes occur, we may be forced to abandon our development efforts for our product candidates, which could significantly harm our business.

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

Clinical trials of SY-1425, SY-5609 or any future product candidates that we, or any future collaborators, may develop will be conducted in carefully defined subsets of patients who have agreed to enter into clinical trials. Consequently, it is possible that our clinical trials, or those of any future collaborator, may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any, or alternatively fail to identify undesirable side effects. If, following approval of a product candidate, we, or others, discover that the product is less effective than previously believed or causes undesirable side effects that were not previously identified, any of the following adverse events could occur:

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

Any of these events could harm our business and operations and could negatively impact our stock price.

Even if our current product candidates, or any future product candidate that we, or any future collaborators, may develop receives marketing approval, it may fail to achieve the degree of market acceptance by physicians, patients, third-party payors and others in the medical community necessary for commercial success, in which case we may not generate significant revenues or become profitable.

We have never commercialized a product, and even if one of our product candidates is approved by the appropriate regulatory authorities for marketing and sale, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. Physicians are often reluctant to switch their patients from existing therapies even when new and potentially more effective or convenient treatments enter the market. Further, patients often acclimate to the therapy that they are currently taking and do not want to switch unless their physicians recommend switching products or they are required to switch therapies due to lack of reimbursement for existing therapies.

Efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may not be successful. If any of our product candidates is approved but does not achieve an adequate level of market acceptance, we may not generate significant revenues 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:

- the efficacy and safety of the product;
- the potential advantages of the product compared to competitive therapies;
- the prevalence and severity of any side effects;

- whether the product is designated under physician treatment guidelines as a first-, second- or third-line therapy;
- our ability, or the ability of any future collaborators, to offer the product for sale at competitive prices;
- the product's convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try, and of physicians to prescribe, the product;
- limitations or warnings, including distribution or use restrictions, contained in the product's approved labeling;
- the strength of sales, marketing and distribution support;
- changes in the standard of care for the targeted indications for the product; and
- availability and amount of coverage and reimbursement from government payors, managed care plans and other third-party payors.

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 resources, we intend to focus on developing product candidates for specific indications that we identify as most likely to succeed, in terms of both their potential for marketing approval and commercialization. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that may prove to have greater commercial potential. For example, in December 2018 we reported data from a pilot cohort of our Phase 2 clinical trial of SY-1425 evaluating the safety and efficacy of SY-1425 in combination with daratumumab, an anti-CD38 antibody approved for the treatment of multiple myeloma. While we reported that SY-1425 in combination with daratumumab was generally well tolerated with no evidence of increased toxicities, and that eight of nine evaluable patients had increased CD38 expression in myeloid blast cells, this expression increased to levels exceeding those of a multiple myeloma cell line in only two of those patients. In order to focus our SY-1425 development activities on the ongoing combination with azacitidine, we announced in January 2019 our portfolio prioritization decision not to pursue further development of SY-1425 in combination with daratumumab beyond completion of this pilot cohort. Similarly, in October 2019 we announced a decision to prioritize development of SY-5609 and to discontinue further development of SY-1365 due to relative potency and selectivity of the two product candidates, comparative preclinical data generated by these product candidates, initial clinical activity and tolerability data from the Phase 1 clinical trial of SY-1365 that did not support an optimal profile for patients, and the emerging treatment landscape focused on oral targeted agents.

Our resource allocation decisions may cause us to fail to capitalize on viable commercial products 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 product candidates. 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 the product candidate.

If we are unable to establish sales, marketing and distribution capabilities or enter into sales, marketing and distribution arrangements with third parties, we may not be successful in commercializing any product candidates if approved.

We do not have a sales, marketing or distribution infrastructure and have no experience in the sale, marketing or distribution of pharmaceutical products. To achieve commercial success for any approved product, we must either develop a sales and marketing organization or outsource these functions to third parties. We plan to build focused capabilities to commercialize development programs for certain indications where we believe that the medical specialists for the indications are sufficiently concentrated to allow us to effectively promote the product with a targeted sales team. The development of sales, marketing and distribution capabilities will require substantial resources, will be 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 and distribution capabilities is delayed or does not occur for any reason, we could have prematurely or unnecessarily incurred these commercialization costs. This may be costly, and our investment could be lost if we cannot retain or reposition our sales and marketing personnel. In addition, we may not be able to hire or retain a sales force that is sufficient in size or has adequate expertise in the medical markets that we plan to target. If we are unable to establish or retain a sales force and marketing and distribution capabilities, our operating results may be adversely affected. If a potential partner has development or commercialization expertise that we believe is particularly relevant to one of our products, then we may seek to collaborate with that potential partner even if we believe we could otherwise develop and commercialize the product independently.

In certain indications, we plan to seek to enter into collaborations that we believe may contribute to our ability to advance development and ultimately commercialize our product candidates. We also intend to seek to enter into collaborations where we believe that realizing the full commercial value of our development programs will require access to broader geographic markets or the pursuit of broader patient populations or indications. As a result of entering into arrangements with third parties to perform sales, marketing and distribution services, our product revenues or the profitability of these product revenues may be lower, perhaps substantially lower, than if we were to directly market and sell products in those markets. Furthermore, we may be unsuccessful in entering into the necessary arrangements with third parties or may be unable to do so on terms that are favorable to us. In addition, we may have little or no control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively.

If we do not establish sales, marketing and distribution capabilities, either on our own or in collaboration with third parties, we will not be successful in commercializing any of our product candidates that receive marketing approval.

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

We expect that we, and any future collaborators, will face significant competition from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide with respect to any of our product candidates that we, or any future collaborators, may seek to develop or commercialize in the future. Specifically, there are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of product candidates for the treatment of the key indications of our most advanced programs. For example, we are aware of several new drugs approved by the FDA since 2018 for the treatment of AML or patient subsets within AML, including ivosidenib, venetoclax, glasdegib and gilteritinib. SY-1425 may also face competition from other investigational products currently in clinical development for AML and MDS, including investigational products in late-stage development from Takeda Pharmaceutical Co. Ltd., Daiichi Sankyo Company, Limited, Agios Pharmaceuticals, Inc., Otsuka Pharmaceutical Co., Ltd., Roche Holding AG, Actinium Pharmaceuticals, Inc., GlycoMimetics, Inc., Arog Pharmaceuticals, Inc., Rafael Pharmaceuticals, Inc., MEI Pharma, Inc., argenx SE in collaboration with Janssen Pharmaceutica NV, Forty Seven, Inc., Aprea Therapeutics, Inc., SELLAS Life Sciences Group, Inc. and Bristol-Myers Squibb Co. In addition, we are aware of selective CDK7 inhibitors being developed in early clinical trials by Carrick Therapeutics Ltd. and Eli Lilly & Co. and several other selective CDK7 inhibitor programs that we believe are in preclinical development, including programs from Aurigene Discovery Technologies Ltd. in collaboration with Exelixis, Inc., Ube Industries Ltd., Qurient Co. Ltd., and Yungjin Pharma Co., Ltd. SY-5609 may face competition from these CDK7 inhibitors. There is also significant competition from products with mechanisms other than CDK7 inhibition in the disease areas where we may choose to focus development of SY-5609 in the future. Our competitors may succeed in developing, acquiring or licensing technologies and products that are more effective, have fewer side effects or more tolerable side effects or are less costly than any product candidates that we are currently developing or that we may develop, which could render our product candidates obsolete and noncompetitive.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer or more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we, or any future collaborators, may develop. For example, the evolving standard of care for the treatment of patients with AML and the response rates and duration of response seen with approved and investigational agents in this disease may result in a longer and more complex clinical development path for SY-1425, which in turn will impact the potential return on investments in clinical trials of SY-1425. Our competitors also may obtain FDA or other marketing approval for their products before we, or any future collaborators, are able to obtain approval for ours, which could result in our competitors establishing a strong market position before we, or any future collaborators, are able to enter the market.

Many of our existing and potential future competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining marketing 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 or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. 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, the development of our product candidates.

Even if we, or any future collaborators, are able to commercialize any product candidate that we, or they, develop, the product may become subject to unfavorable pricing regulations, third-party payor reimbursement practices or healthcare reform initiatives, any of which could 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 care programs and private health insurers. If coverage is not available, or reimbursement is limited, we, or any future collaborators, may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us, or any future collaborators, to establish or maintain pricing sufficient to realize a sufficient return on our or their investments. In the United States, no uniform policy of coverage and reimbursement for products exists among third-party payors and coverage and reimbursement levels 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 may require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

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

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

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

In addition, increasingly, third-party payors are requiring higher levels of evidence of the benefits and clinical outcomes of new technologies and are challenging the prices charged. Further, the net reimbursement for drug products may be subject to additional reductions if there are changes to laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. An inability to promptly obtain coverage and adequate payment rates from both government-funded and private payors for any of our product candidates for which we, or any future collaborator, obtain marketing approval could significantly harm our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

Product liability lawsuits against us could divert our resources, cause us to incur substantial liabilities and limit commercialization of any products that we may develop.

We will face an inherent risk of product liability claims as a result of the clinical testing of our product candidates despite obtaining appropriate informed consents from our clinical trial participants. We will face an even greater risk if we or any future collaborators commercially sell any product that we may or they may develop. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our product candidates or products that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend resulting litigation;
- substantial monetary awards to trial participants or patients;
- loss of revenue;
- reduced resources of our management to pursue our business strategy; and
- the inability to commercialize any products that we may develop.

Although we maintain clinical trial liability insurance coverage in the amount of up to $5.0 million in the aggregate, this insurance may not fully cover potential liabilities that we may incur. The cost of any product liability litigation or other proceeding, even if resolved in our favor, could be substantial. We will need to increase our insurance coverage if and when we commercialize any product that receives marketing approval. In addition, insurance coverage is becoming increasingly expensive. If we are unable to obtain or maintain sufficient insurance coverage at an acceptable cost or to otherwise protect against potential product liability claims, it could prevent or inhibit the development and commercial production and sale of our product candidates, which could harm our business, financial condition, results of operations and prospects.

If the FDA or comparable foreign regulatory authorities approve generic versions of any of our products that receive marketing approval, or such authorities do 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.

Once an NDA is approved, the product covered thereby becomes 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 branded product or reference-listed drug may be typically lost to the generic product.

The FDA may not approve an ANDA for a generic product until any applicable period of non-patent exclusivity for the reference-listed drug has expired. The Federal Food, Drug, and Cosmetic Act, or FDCA, provides a period of five years of non-patent exclusivity for a new drug containing a new chemical entity, or NCE. Specifically, in cases where such exclusivity has been granted, an ANDA may not be filed with the FDA until the expiration of five years unless the submission is accompanied by a Paragraph IV certification that a patent covering the reference-listed drug is either invalid or will not be infringed by the generic product, in which case the applicant may submit its application four years following approval of the reference-listed drug. Because the composition of matter patent for SY-1425 has expired and our license rights to SY-1425 from TMRC are limited to human cancer indications, it is possible that another applicant could obtain

approval of tamibarotene from the FDA before us, in which case our NDA would not be eligible for NCE exclusivity. See "—Risks Related to Our Intellectual Property—We do not have composition of matter patent protection with respect to SY-1425." If any product we develop does not receive five years of NCE exclusivity, the FDA may approve generic versions of such product three years after its date of approval, subject to the requirement that the ANDA applicant certifies to any patents listed for our products in the Orange Book. Manufacturers may seek to launch these generic products following the expiration of the applicable marketing exclusivity period, even if we still have patent protection for our product.

Competition that our products may face from generic versions of our products 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.

Risks Related to Our Dependence on Third Parties

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

We expect to rely on third parties, such as contract research organizations, clinical data management organizations, medical institutions and clinical investigators, to conduct our clinical trials. We currently rely and expect to continue to rely on third parties to conduct certain aspects of our research and preclinical testing. Any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it would delay our product development activities.

Our reliance on these third parties for research and development activities will reduce our control over these activities, but will not relieve us of our responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with standards, commonly referred to as good clinical practices, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will 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 expect 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 currently depend on third-party manufacturers to produce our preclinical and clinical drug supplies and we intend to rely upon third-party manufacturers to produce commercial supplies of any approved product candidates.

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

We do not currently have a long-term supply agreement with any third-party manufacturers. We may be unable to establish any agreements with third-party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

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

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

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

We have engaged, and expect to continue engaging, third-party suppliers and manufacturers in China and India. Natural disasters such as earthquakes, tsunamis, power shortages or outages, floods or monsoons, public health crises such as pandemics and epidemics, political crises such as terrorism, war, political insecurity or other conflict, or other events outside of our control could adversely affect the ability of these third parties to perform their obligations as expected. For example, in December 2019 a strain of coronavirus known as COVID-19 was reported to have surfaced in Wuhan, China, resulting in business closures throughout China. Whether or how these business closures may affect our third-party suppliers and manufacturers in China, and therefore our ability to manufacture preclinical and clinical drug supplies, remains uncertain.

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 of 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.

To the extent that we enter into collaborations with third parties for the development and commercialization of any product candidates, our prospects with respect to those product candidates will depend in significant part on the success of those collaborations.

We expect to enter into collaborations for the development and commercialization of one or more product candidates we may develop, or to use our gene control platform to identify and validate disease targets, as we have with GBT to develop novel therapies for sickle cell disease and beta thalassemia and with Incyte to identify new drug targets in the field of myeloproliferative neoplasms. To the extent we enter into such collaborations, we will have limited control over the amount and timing of resources that our collaborators will dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on any collaborators' abilities to successfully perform the functions assigned to them in these arrangements. In addition, collaborators may have the right to abandon research or development projects and terminate applicable agreements, including funding obligations, prior to or upon the expiration of the agreed upon terms.

Collaborations involving our product candidates pose a number of risks, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- 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 collaborators' strategic focus or available funding or external factors, such as an acquisition, that divert resources or create competing priorities;
- 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;

- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates;

- a collaborator with marketing and distribution rights to one or more products may not commit sufficient resources to the marketing and distribution of such product or products;

- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or termination of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time consuming and expensive;

- 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 intellectual property or proprietary information or expose us to potential litigation;

- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; and

- 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.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If any future collaborator of ours is involved in a business combination, it could decide to delay, diminish or terminate the development or commercialization of any product candidate licensed to it by us.

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

We expect to seek one or more additional collaborators for the development and commercialization of one or more of our product candidates or to validate targets. Likely collaborators may include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. In addition, if we are able to obtain marketing approval for product candidates from foreign regulatory authorities, we intend to enter into strategic relationships with international biotechnology or pharmaceutical companies for the commercialization of such product candidates outside of the United States.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration, and the proposed collaborator's evaluation of a number of factors. Those factors may include the potential differentiation of our product candidates from competing product candidates, design or results of clinical trials, the likelihood of approval by the FDA or comparable foreign regulatory authorities and the regulatory pathway for any such approval, the potential market for the product candidate, the costs and complexities of manufacturing and delivering the product to patients and the potential of competing products. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available for collaboration and whether such a collaboration could be more attractive than the one with us for our product candidate. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue.

Collaborations are complex and time consuming to negotiate and document.

Our collaboration agreements with GBT and Incyte contain, and any collaboration agreement that we enter into in the future may contain, restrictions on our ability to enter into potential collaborations, to conduct research or development in certain fields, or to otherwise develop specified product candidates. Further, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators. We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of the product candidate for which we are seeking to collaborate, reduce or delay our development program or one or more of our other development programs, delay our potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense.

Risks Related to Our Intellectual Property

If we fail to comply with our obligations under our existing and any future intellectual property licenses with third parties, we could lose license rights that are important to our business.

We are party to several license agreements under which we license patent rights and other intellectual property related to our business, including the TMRC license agreement, pursuant to which we were granted a license under specified patent rights, data, regulatory filings and other intellectual property for the North American and European development and commercialization of SY-1425 for the treatment of human cancer indications. We may enter into additional license agreements in the future. Our license agreements impose, and we expect that future license agreements will impose, various diligence, milestone payment, royalty, insurance and other obligations on us. If we fail to comply with our obligations under these licenses, our licensors may have the right to terminate these license agreements, in which event we might not be able to market any product that is covered by these agreements, or our licensors may convert the license to a non-exclusive license, which could adversely affect the value of the product candidate being developed under the license agreement. Termination of these license agreements or reduction or elimination of our licensed rights may also result in our having to negotiate new or reinstated licenses with less favorable terms.

We do not have composition of matter patent protection with respect to SY-1425.

We own certain patents and patent applications with claims directed to specific methods of using SY-1425 and we expect to have marketing exclusivity from the FDA and EMA for a period of no less than five and ten years, respectively, because tamibarotene, the active pharmaceutical ingredient of SY-1425, has not been approved in these markets. Composition of matter patent protection in the United States and elsewhere covering SY-1425 has expired, however. We may be limited in our ability to list our method patents in the FDA's Orange Book if the use of our product, consistent with its FDA-approved label, would not fall within the scope of our patent claims. Also, our competitors may be able to offer and sell products so long as these competitors do not infringe any other patents that we (or third parties) hold, including patents with claims directed to the manufacture of SY-1425 and/or method of use patents. In general, method of use patents are more difficult to enforce than composition of matter patents because, for example, of the risks that the FDA may approve alternative uses of the subject compounds not covered by the method of use patents, and others may engage in off-label sale or use of the subject compounds. Physicians are permitted to prescribe an approved product for uses that are not described in the product's labeling. Although off-label prescriptions may infringe our method of use patents, the practice is common across medical specialties and such infringement is difficult to prevent or prosecute. FDA approval of uses of a generic version of SY-1425 that are not covered by our patents would limit our ability to generate revenue from the sale of SY-1425, if approved for commercial sale. In addition, any off-label use of a generic version of SY-1425 would limit our ability to generate revenue from the sale of SY-1425, if approved for commercial sale.

Our intellectual property licenses with third parties may be subject to disagreements over contract interpretations, which could narrow the scope of our rights to the relevant intellectual property or technology or increase our financial or other obligations to our licensors.

The agreements under which we currently license intellectual property or technology from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could harm our business, financial condition, results of operations and prospects.

We may not be successful in obtaining or maintaining necessary rights to current or future product candidates through acquisitions and in-licenses.

We currently have rights to certain intellectual property, through ownership or licenses from third parties, to develop and commercialize SY-1425 for human cancers in North America and Europe, and SY-5609 for all potential uses worldwide. Because our programs may require the use of proprietary rights by third parties, the growth of our business likely will depend, in part, on our ability to acquire, in-license or use these proprietary rights. We may be unable to acquire or in-license any compositions, methods of use, processes or other intellectual property rights from third parties that we identify as necessary for any product candidates. The licensing or acquisition of third-party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third-party intellectual property rights that we may consider attractive. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment.

We sometimes collaborate with non-profit and academic institutions to accelerate our preclinical research or development under written agreements with these institutions. Typically, these institutions provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Regardless of such option, we may be unable to negotiate a license within the specified timeframe or under terms that are acceptable to us or we may decide not to execute such option if we believe such license is not necessary to pursue our program. If we are unable or opt not to do so, the institution may offer the intellectual property rights to other parties, potentially blocking our ability to pursue our program.

If we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may be required to expend significant time and resources to redesign our product candidates or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize the affected product candidate, which could harm our business significantly.

We depend upon our license with TMRC, and we may not be able to maintain that license.

We have entered into a standby license with TMRC and Toko Pharmaceuticals Ind. Co. Ltd., or Toko, providing that if at any time the license agreement between Toko and TMRC relating to the SY-1425 rights that TMRC has licensed to us terminates or otherwise ceases to be in effect for any reason, Toko will grant directly to us such rights and licenses with respect to SY-1425 as are necessary for us to continue to develop SY-1425. If the TMRC license agreement terminates and this standby license terminates, then we may lose rights to SY-1425 that may be necessary to the development and commercialization of SY-1425, which could have a material adverse impact on our business.

If we are unable to obtain and maintain sufficient patent protection for any product candidates, or if the scope of the patent protection is not sufficiently broad, our competitors could develop and commercialize products similar or identical to ours, and our ability to successfully commercialize our product candidates 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 product candidates. If we do not adequately protect our intellectual property, our competitors may be able to erode or negate any competitive advantage we may have, which could harm our business and ability to achieve profitability. To protect our proprietary position, we file patent applications in the United States and abroad related to our novel product candidates that are important to our business. We also license or purchase patent applications filed by others. The patent application and approval process is expensive and time consuming. We may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner.

Agreements through which we license patent rights may not give us control over patent prosecution or maintenance, so that we may not be able to control which claims or arguments are presented and may not be able to secure, maintain, or successfully enforce necessary or desirable patent protection from those patent rights. We have not had and do not have primary control over patent prosecution and maintenance for certain of the patents and patent applications we license, and therefore cannot guarantee that these patents and applications will be prosecuted in a manner consistent with the best interests of our business. We cannot be certain that patent prosecution and maintenance activities by our licensors have been or will be conducted in compliance with applicable laws and regulations or will result in valid and enforceable patents.

We, or any future partners, collaborators or licensees, may fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection for them. Therefore, we may miss potential opportunities to strengthen our patent position.

It is possible that defects of form in the preparation or filing of our patents or patent applications may exist, or may arise in the future, for example with respect to proper priority claims, inventorship, claim scope or patent term adjustments. If we or our partners, collaborators, licensees, or licensors, whether current or future, fail to establish, maintain or protect such patents and other intellectual property rights, such rights may be reduced or eliminated. If our partners, collaborators, licensees or licensors, are not fully cooperative or disagree with us as to the prosecution, maintenance or enforcement of any patent rights, such patent rights could be compromised. If there are material defects in the form, preparation, prosecution, or enforcement of our patents or patent applications, such patents may be invalid and/or unenforceable, and such applications may never result in valid, enforceable patents. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain. No consistent policy regarding the breadth of claims allowed in biotechnology and pharmaceutical patents has emerged to date in the United States or in many foreign jurisdictions. In addition, the determination of patent rights with respect to pharmaceutical compounds commonly involves complex legal and factual questions, which 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.

Pending patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until a patent issues from such applications. Assuming the other requirements for patentability are met, currently, the first to file a patent application is generally entitled to the patent except that, prior to March 16, 2013 in the United States, the first to invent was entitled to the patent. 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 patents or pending patent applications, or that we were the first to file for patent protection of such inventions. Similarly, we cannot be certain that parties from whom we do or may license or purchase patent rights were the first to make relevant claimed inventions, or were the first to file for patent protection for them. If third parties have filed patent applications on inventions claimed in our patents or applications on or before March 15, 2013, an interference proceeding in the United States can be initiated by such third parties to determine who was the first to invent any of the subject matter covered by the patent claims of our applications. If third parties have filed such applications after March 15, 2013, a derivation proceeding in the United States can be initiated by such third parties to determine whether our invention was derived from theirs.

Moreover, because the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, our patents or pending patent applications may be challenged in the courts or patent offices in the United States and abroad. There is no assurance that all of the potentially relevant prior art relating to our patents and patent applications has been found. If such prior art exists, it may be used to invalidate a patent, or may prevent a patent from issuing from a pending patent application. For example, such patent filings may be subject to a third-party preissuance submission of prior art to the U.S. Patent and Trademark Office, or USPTO, or to other patent offices around the world. Alternately or additionally, we may become involved in post-grant review procedures, oppositions, derivations, proceedings, reexaminations, *inter partes* review or interference proceedings, in the United States or elsewhere, challenging patents or patent applications in which we have rights, including patents on which we rely to protect our business. An adverse determination in any such challenges may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, 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 products. In addition, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized.

Pending and future patent applications may not result in patents being issued which protect our business, in whole or in part, or which effectively prevent others from commercializing competitive products. 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. In addition, the laws of foreign countries may not protect our rights to the same extent or in the same manner as the laws of the United States.

Issued patents that we have or may obtain or license may not provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner. Our competitors may also seek approval to market their own products similar to or otherwise competitive with our products. Alternatively, our competitors may seek to market generic versions of any approved products by submitting ANDAs to the FDA in which they claim that patents owned or licensed by us are invalid, unenforceable or not infringed. In these circumstances, we may need to defend or assert our patents, or both, including by filing lawsuits alleging patent infringement. In any of these types of proceedings, a court or other agency with jurisdiction may find our patents invalid or unenforceable, or that our competitors are competing in a non-infringing manner. Thus, even if we have valid and enforceable patents, these patents still may not provide protection against competing products or processes sufficient to achieve our business objectives.

Pursuant to the terms of some of our license agreements with third parties, some of our third-party licensors have the right, but not the obligation, in certain circumstances to control enforcement of our licensed patents or defense of any claims asserting the invalidity of these patents. Even if we are permitted to pursue such enforcement or defense, we will require the cooperation of our licensors, and cannot guarantee that we would receive it and on what terms. We cannot be certain that our licensors will allocate sufficient resources or prioritize their or our enforcement of such patents or defense of such claims to protect our interests in the licensed patents. If we cannot obtain patent protection, or enforce existing or future patents against third parties, our competitive position and our financial condition could suffer.

If we are unable to protect the confidentiality of our trade secrets, the value of our technology could be materially adversely affected and our business would be harmed.

In addition to the protection afforded by patents, we also rely on trade secret protection for certain aspects of our technology platform, including certain aspects of our gene control platform. We seek to protect these trade secrets, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, consultants, independent contractors, advisors, contract manufacturers, suppliers and other third parties. We also enter into confidentiality and invention or patent assignment agreements with employees and certain consultants. Any party with whom we have executed such an agreement may breach that agreement and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time consuming, and the outcome is unpredictable. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating the trade secret. Further, if any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent such third party, or those to whom they communicate such technology or information, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our business and competitive position could be harmed.

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

Competitors may infringe our patents, trademarks, copyrights or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming and divert the time and attention of our management and scientific personnel. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents, in addition to counterclaims asserting that our patents are invalid or unenforceable, or both. In any patent infringement proceeding, there is a risk that a court will decide that a patent of ours is invalid or unenforceable, in whole or in part, and that we do not have the right to stop the other party from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent's claims narrowly or decide that we do not have the right to stop the other party from using the invention at issue on the grounds that our patent claims do not cover the invention. An adverse outcome in a litigation or proceeding involving one or more of our patents could limit our ability to assert those patents against those parties or other competitors and may curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. Similarly, if we assert trademark infringement claims, a court may determine that the marks we have asserted are invalid or unenforceable, or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In this case, we could ultimately be forced to cease use of such trademarks.

Even if we establish infringement, the court may decide not to grant an injunction against further infringing activity and instead award only monetary damages, which may or may not be an adequate remedy. 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 litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could adversely affect the price of shares of our common stock. Moreover, there can be no assurance that we will have sufficient financial or other resources to file and pursue such infringement claims, which typically last for years before they are concluded. Even if we ultimately prevail in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings.

If we are sued for infringing intellectual property rights of third parties, such litigation could be costly and time consuming and could prevent or delay us from developing or commercializing our product candidates.

Our commercial success depends, in part, on our ability to develop, manufacture, market and sell our product candidates and use our gene control technology without infringing the intellectual property and other proprietary rights of third parties. Third parties may have U.S. and non-U.S. issued patents and pending patent applications relating to compounds and methods of use for the treatment of the disease indications for which we are developing our product candidates. If any third-party patents or patent applications are found to cover our product candidates or their methods of use, we may not be free to manufacture or market our product candidates as planned without obtaining a license, which may not be available on commercially reasonable terms, or at all.

There is a substantial amount of intellectual property litigation in the biotechnology and pharmaceutical industries, and we may become party to, or threatened with, litigation or other adversarial proceedings regarding intellectual property rights with respect to our product candidates, including interference proceedings before the USPTO. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates. Because patent applications can take many years to issue, there may be currently pending patent applications which may later result in issued patents that our product candidates may be accused of infringing. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. Accordingly, third parties may assert infringement claims against us based on existing or future intellectual property rights. The outcome of intellectual property litigation is subject to uncertainties that cannot be adequately quantified in advance. The pharmaceutical and biotechnology industries have produced a significant number of patents, and it may not always be clear to industry participants, including us, which patents cover various types of products or methods of use. The coverage of patents is subject to interpretation by the courts, and the interpretation is not always uniform. If we were sued for patent infringement, we would need to demonstrate that our product candidates, products or methods either do not infringe the patent claims of the relevant patent or that the patent claims are invalid or unenforceable, and we may not be able to do this. Proving invalidity is difficult. For example, in the United States, proving invalidity requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and scientific personnel could be diverted in pursuing these proceedings, which could significantly harm our business and operating results. In addition, we may not have sufficient resources to bring these actions to a successful conclusion.

If we are found to infringe a third party's intellectual property rights, we could be forced, including by court order, to cease developing, manufacturing or commercializing the infringing product candidate or product. Alternatively, we may be required to obtain a license from such third party in order to use the infringing technology and continue developing, manufacturing or marketing the infringing product candidate or product. It is possible, however, that we would be unable to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. Alternatively or additionally, it could include terms that impede or destroy our ability to compete successfully in the commercial marketplace. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

Changes to the patent law in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products.

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involves both technological and legal complexity and is therefore costly, time consuming and inherently uncertain. Recent patent reform legislation in the United States, including the Leahy-Smith America Invents Act, or the America Invents Act, could increase those uncertainties and costs. The America Invents Act was signed into law on September 16, 2011, and many of the substantive changes became effective on March 16, 2013. The America Invents Act reforms United States patent law in part by changing the U.S. patent system from a "first to invent" system to a "first inventor to file" system, expanding the definition of prior art, and developing a post-grant review system. This legislation changes United States patent law in a way that may weaken our ability to obtain patent protection in the United States for those applications filed after March 16, 2013.

Further, the America Invents Act created new procedures to challenge the validity of issued patents in the United States, including post-grant review and *inter partes* review proceedings, which some third parties have been using to cause the cancellation of selected or all claims of issued patents of competitors. For a patent with an effective filing date of March 16, 2013 or later, a petition for post-grant review can be filed by a third party in a nine-month window from issuance of the patent. A petition for *inter partes* review can be filed immediately following the issuance of a patent if the patent has an effective filing date prior to March 16, 2013. A petition for *inter partes* review can be filed after the nine-month period for filing a post-grant review petition has expired for a patent with an effective filing date of March 16, 2013 or later. Post-grant review proceedings can be brought on any ground of invalidity, whereas *inter partes* review proceedings can only raise an invalidity challenge based on published prior art and patents. These adversarial actions at the USPTO review patent claims without the presumption of validity afforded to U.S. patents in lawsuits in U.S. federal courts and use a lower burden of proof than used in litigation in U.S. federal courts. Therefore, it is generally considered easier for a competitor or third party to have a U.S. patent invalidated in a USPTO post-grant review or *inter partes* review proceeding than invalidated in a litigation in a U.S. federal court. If any of our patents are challenged by a third party in such a USPTO proceeding, there is no guarantee that we or our licensors or collaborators will be successful in defending the patent, which would result in a loss of the challenged patent right to us.

In addition, the USPTO continues to modify its guidelines regarding subject matter eligibility, a process that began with decisions rendered in *Association for Molecular Pathology v. Myriad Genetics, Inc*.; *BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litigation*; and *Promega Corp. v. Life Technologies Corp.* Those court decisions have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents once obtained. Depending on future actions by the U.S. Congress, the U.S. courts, the USPTO and the relevant law-making bodies in other countries, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

We may not be able to enforce our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on our product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. The requirements for patentability may differ in certain countries, particularly in developing countries; thus, even in countries where we do pursue patent protection, there can be no assurance that any patents will issue with claims that cover our products.

Moreover, our ability to protect and enforce our intellectual property rights may be adversely affected by unforeseen changes in foreign intellectual property laws. Additionally, laws of some countries outside of the United States and Europe do not afford intellectual property protection to the same extent as the laws of the United States and Europe. Many companies have encountered significant problems in protecting and defending intellectual property rights in certain foreign jurisdictions. The legal systems of some countries, including India, China and other developing countries, do not favor the enforcement of patents and other intellectual property rights. This could make it difficult for us to stop the infringement of our patents or the misappropriation of our other intellectual property rights. For example, many foreign countries have compulsory licensing laws under which a patent owner must grant licenses to third parties. Consequently, we may not be able to prevent third parties from practicing our inventions in certain countries outside the United States and Europe. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop and market their own products and, further, may export otherwise infringing products to territories where we have patent protection, if our ability to enforce our patents to stop infringing activities is inadequate. These products may compete with our products, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Agreements through which we license patent rights may not give us sufficient rights to permit us to pursue enforcement of our licensed patents or defense of any claims asserting the invalidity of these patents (or control of enforcement or defense) of such patent rights in all relevant jurisdictions as requirements may vary.

Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, could result in substantial costs and divert our efforts and resources from other aspects of our business. Moreover, such proceedings could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Furthermore, while we intend to protect our intellectual property rights in major markets for our products, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our products. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate.

Patent terms may be inadequate to protect our competitive position on our products for an adequate amount of time.

Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. We expect to seek extensions of patent terms in the United States and, if available, in other countries where we are prosecuting patents. In the United States, the Drug Price Competition and Patent Term Restoration Act of 1984 permits a patent term extension of up to five years beyond the normal expiration of the patent, which is limited to the approved indication (or any additional indications approved during the period of extension). The applicable authorities, including the FDA and the USPTO in the United States, and any equivalent regulatory authority in other countries, may not agree, however, with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. If this occurs, our competitors may be able to take advantage of our investment in development and clinical trials by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case.

We may be subject to claims by third parties asserting that our employees or we have misappropriated their intellectual property or claiming ownership of what we regard as our own intellectual property.

Many of our employees and our licensors' employees, including our senior management, were previously employed at universities or at other biotechnology or pharmaceutical companies, some of which may be competitors or potential competitors. Some of these employees, including each member of our senior management, executed proprietary rights, non-disclosure and non-competition agreements, or similar agreements, in connection with such previous employment. Although we try to ensure that our employees 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 employees have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such third party. Litigation may be necessary to defend against such claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel or sustain damages. Such intellectual property rights could be awarded to a third party, and we could be required to obtain a license from such third party to commercialize our technology or products. Such a license may not be available on commercially reasonable terms or at all. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

In addition, while we typically require our employees, consultants, contractors and vendors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own, which may result in claims by or against us related to the ownership of such intellectual property. If we fail in prosecuting or defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights. Even if we are successful in prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to our senior management and scientific personnel.

Obtaining and maintaining patent protection depends on compliance with various procedural, document submission, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and applications are required to be paid to the USPTO and various governmental patent agencies outside of the United States in several stages over the lifetime of the patents and applications. The USPTO and various non-U.S. governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process and after a patent has issued. There are situations in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction.

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

Even if we complete the necessary preclinical studies and clinical trials, the regulatory approval process is expensive, time consuming and uncertain and may prevent us or any future collaborators from obtaining approvals for the commercialization of some or all of our product candidates. As a result, we cannot predict when or if, and in which territories, we, or any future collaborators, will obtain marketing approval to commercialize a product candidate.

The research, testing, manufacturing, labeling, approval, selling, marketing, promotion and distribution of products are subject to extensive regulation by the FDA and comparable foreign regulatory authorities. We, and any future collaborators, are not permitted to market our product candidates in the United States or in other countries until we, or they, receive approval of an NDA from the FDA or marketing approval from applicable regulatory authorities outside the United States. Our product candidates are in various stages of development and are subject to the risks of failure inherent in drug development. We have not submitted an application for or received marketing approval for any of our product candidates in the United States or in any other jurisdiction. We have limited experience in conducting and managing the clinical trials necessary to obtain marketing approvals, including FDA approval of an NDA.

The process of obtaining marketing approvals, both in the United States and abroad, is lengthy, expensive and uncertain. It may take many years, 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. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities. The FDA or other regulatory authorities may determine that our product candidates are not safe and effective, only moderately effective or have undesirable or unintended side effects, toxicities or other characteristics that preclude our obtaining marketing approval or prevent or limit commercial use. Moreover, the FDA or other regulatory authorities may fail to approve the companion diagnostics we contemplate developing with partners. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

In addition, changes in marketing approval policies during the development period, changes in or the enactment or promulgation of additional statutes, regulations or guidance or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we, or any future collaborators, ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

Any delay in obtaining or failure to obtain required approvals could negatively affect our ability or that of any future collaborators to generate revenue from the particular product candidate, which likely would result in significant harm to our financial position and adversely impact our stock price.

If we are required by the FDA to obtain approval of a companion diagnostic in connection with approval of a candidate therapeutic product, and we do not obtain or there are delays in obtaining FDA approval of a diagnostic device, we will not be able to commercialize the product candidate and our ability to generate revenue will be materially impaired.

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, 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 is not also approved or cleared for that indication. Under the Federal Food, Drug, and Cosmetic Act, or FDCA, companion diagnostics are regulated as medical devices and the FDA has generally required companion diagnostics intended to select the patients who will respond to cancer treatment to obtain premarket approval, or a PMA. Consequently, we anticipate that certain of our companion diagnostics may require us or our collaborators to obtain a PMA. The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, 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 approval is not guaranteed and may take considerable time, 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. As a result, if we or our collaborators are required by the FDA to obtain approval of a companion diagnostic for a candidate therapeutic product, and we or our collaborators do not obtain or there are delays in obtaining FDA approval of a diagnostic device, we will not be able to commercialize the product candidate and our ability to generate revenue will be materially impaired.

In its August 2014 guidance, the FDA also indicated that companion diagnostics used to make treatment decisions in clinical trials of a therapeutic product generally will be considered investigational devices. When a companion diagnostic is used to make critical treatment decisions, such as patient selection, the FDA stated that the diagnostic will be considered a significant risk device requiring an investigational device exemption. The FDA may find that a companion diagnostic that we, alone or with a third party, plan to develop does not comply with those requirements and, if this were to occur, we would not be able to proceed with our planned trial of the applicable product candidate in these patient populations.

Failure to obtain marketing approval in foreign jurisdictions would prevent our product candidates from being marketed abroad. Any approval we are granted for our product candidates in the United States would not assure approval of our product candidates in foreign jurisdictions.

In order to market and sell our products in the European Union and other foreign jurisdictions, we, and any future 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 marketing 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, and any future collaborators, may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. We may file for marketing approvals but not receive necessary approvals to commercialize our products in any market.

Additionally, on June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as Brexit. Following protracted negotiations, the United Kingdom left the European Union on January 31, 2020. Under the withdrawal agreement, there is a transitional period until December 31, 2020 (extendable up to two years). Discussions between the United Kingdom and the European Union have so far mainly focused on finalizing withdrawal issues and transition agreements but have been extremely difficult to date. The Prime Minister of the United Kingdom has indicated that the United Kingdom will not accept high regulatory alignment with the European Union. 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 European Union 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. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom and/or the European Union 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 European Union for our product candidates, which could significantly and materially harm our business.

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

Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs 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 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. We have obtained orphan drug designation for SY-1425 for the treatment of AML in the United States and in Europe. In the future, however, we or any future collaborators may seek orphan drug designations for SY-1425 in other indications or territories or for other product candidates and may be unable to obtain such designations.

Even if we, or any future collaborators, obtain orphan drug designation for a product candidate, we, or they, may not be able to obtain orphan drug exclusivity for that product candidate. Generally, a product with orphan drug designation only becomes entitled to orphan drug exclusivity if it receives the first marketing approval for the indication for which it has such designation, in which case the FDA or the EMA will be precluded from approving another marketing application for the same drug for that indication for the applicable exclusivity period. The applicable exclusivity 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 drug no longer meets the criteria for orphan drug designation or if the drug is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be lost if the FDA or the EMA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition.

Even if we, or any future collaborators, obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs can be approved for the same condition and the same drug can be approved for different conditions. Even after an orphan drug is approved, the FDA can subsequently approve the same drug for the same condition if the FDA concludes that the later drug is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care.

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

Even if we, or any future collaborators, obtain marketing approvals for our product candidates, the terms of approvals and ongoing regulation of our products may limit how we manufacture and market our products, which could impair our ability to generate revenue.

Once marketing approval has been granted, an approved product and its manufacturer and marketer are subject to ongoing review and extensive regulation. We, and any future collaborators, must therefore comply with requirements concerning advertising and promotion for any of our product candidates for which we or they obtain marketing approval. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved labeling. Thus, we and any future collaborators will not be able to promote any products we develop for indications or uses for which they are not approved.

In addition, manufacturers of approved products and those manufacturers' facilities are required to comply with extensive FDA requirements, including ensuring that quality control and manufacturing procedures conform to cGMPs, which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements. We, our contract manufacturers, any future collaborators and their contract manufacturers could be subject to periodic unannounced inspections by the FDA to monitor and ensure compliance with cGMPs.

Accordingly, assuming we, or any future collaborators, receive marketing approval for one or more of our product candidates, we, and any future collaborators, and our and their contract manufacturers will continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance and quality control.

If we, and any future collaborators, are not able to comply with post-approval regulatory requirements, we, and any future collaborators, could have the marketing approvals for our products withdrawn by regulatory authorities and our, or any future collaborators', ability to market any future products could be limited, which could adversely affect our ability to achieve or sustain profitability. Further, the cost of compliance with post-approval regulations may have a negative effect on our operating results and financial condition.

Any of our product candidates for which we, or any future collaborators, obtain marketing approval in the future could be subject to post-marketing restrictions or withdrawal from the market and we, or any future collaborators, may be subject to substantial penalties if we, or they, fail to comply with regulatory requirements or if we, or they, experience unanticipated problems with our products following approval.

Any of our product candidates for which we, or any future collaborators, obtain marketing approval, as well as the manufacturing processes, post-approval studies and measures, labeling, advertising and promotional activities for such product, among other things, will be subject to ongoing 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, requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, including the requirement to implement a Risk Evaluation and Mitigation Strategy.

The FDA may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of a product. The FDA and other agencies, including the Department of Justice, closely regulate and monitor the post-approval marketing and promotion of products to ensure that they are manufactured, marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding off-label use and if we, or any future collaborators, do not market any of our product candidates for which we, or they, receive marketing approval for only their approved indications, we, or they, may be subject to warnings or enforcement action for off-label marketing. Violation of the FDCA and other statutes, including the False Claims Act, relating to the promotion and advertising of prescription drugs may lead to investigations or allegations of violations of federal and state health care fraud and abuse laws and state consumer protection laws.

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

- restrictions on such products, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- restrictions on coverage by third-party payors;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of products;
- product seizure; or
- injunctions or the imposition of civil or criminal penalties.

We may seek a Breakthrough Therapy designation for one or more of our product candidates, but we might not receive such designation, and even if we do, such designation may not lead to a faster development or regulatory review or approval process.

We may seek a Breakthrough Therapy designation for one or more of our product candidates. A Breakthrough Therapy is defined as a product that is intended, alone or in combination with one or more other products, to treat a serious 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. For products that have been designated as Breakthrough Therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Products designated as Breakthrough Therapies by the FDA may also be eligible for priority review if supported by clinical data at the time the NDA is submitted to the FDA.

Designation as a Breakthrough Therapy is within the discretion of the FDA. Accordingly, even if we believe that one of our product candidates meets the criteria for designation as a Breakthrough Therapy, the FDA may disagree and instead determine not to make such designation. Even if we receive Breakthrough Therapy designation, the receipt of such designation for a product candidate may not result in a faster development or regulatory review or approval process compared to products considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as Breakthrough Therapies, the FDA may later decide that the product candidates no longer meet the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

We may seek Fast Track designation for one or more of our product candidates, but we might not receive such designation, and even if we do, such designation may not actually lead to a faster development or regulatory review or approval process.

If a product is intended for the treatment of a serious condition and nonclinical or clinical data demonstrate the potential to address unmet medical need for this condition, a product sponsor may apply for FDA Fast Track designation. If we seek Fast Track designation for a product candidate, we may not receive it from the FDA. Even if we receive Fast Track designation, however, Fast Track designation does not ensure that we will receive marketing approval or that approval will be granted within any particular timeframe. We may not experience a faster development or regulatory review or approval process with Fast Track designation compared to conventional FDA procedures. In addition, the FDA may withdraw Fast Track designation if it believes that the designation is no longer supported by data from our clinical development program. Fast Track designation alone does not guarantee qualification for the FDA's priority review procedures.

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

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

We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. For example, certain policies of the Trump Administration may impact our business and industry. Namely, the Trump Administration has taken several executive actions, including the issuance of a number of Executive Orders, that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine regulatory and oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. An under-staffed FDA could result in delays in the FDA's responsiveness or in its ability to review submissions or applications, issue regulations or guidance, or implement or enforce regulatory requirements in a timely fashion or at all. Moreover, on January 30, 2017, President Trump issued an Executive Order, applicable to all executive agencies, including the FDA, which requires that for each notice of proposed rulemaking or final regulation to be issued in fiscal year 2017, the agency shall identify at least two existing regulations to be repealed, unless prohibited by law. These requirements are referred to as the "two-for-one" provisions. This Executive Order includes a budget neutrality provision that requires the total incremental cost of all new regulations in the 2017 fiscal year, including repealed regulations, to be no greater than zero, except in limited circumstances. For fiscal years 2018 and beyond, the Executive Order requires agencies to identify regulations to offset any incremental cost of a new regulation and approximate the total costs or savings associated with each new regulation or repealed regulation. In interim guidance issued by the Office of Information and Regulatory Affairs within Office of Management and Budget on February 2, 2017, the administration indicates that the "two-for-one" provisions may apply not only to agency regulations, but also to significant agency guidance documents. In addition, on February 24, 2017, President Trump issued an executive order directing each affected agency to designate an agency official as a "Regulatory Reform Officer" and establish a "Regulatory Reform Task Force" to implement the two-for-one provisions and other previously issued executive orders relating to the review of federal regulations, however it is difficult to predict how these requirements will be implemented, and the extent to which they will impact the FDA's ability to exercise its regulatory authority. If these executive actions impose constraints on the FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted

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

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

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

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

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. These changes include the Budget Control Act of 2011, which, among other things, led to aggregate reductions to Medicare payments to providers of up to 2% per fiscal year that started in 2013 and, due to subsequent legislative amendments to the statute, will stay in effect through 2025 unless additional congressional action is taken, and the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Further, there have been several recent U.S. congressional inquiries and proposed state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products.

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

With enactment of the Tax Cuts and Jobs Act of 2017, which was signed by President Trump on December 22, 2017, Congress repealed the “individual mandate.” The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, will become effective in 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. Moreover, on December 14, 2018, a U.S. District Court judge in the Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and inseverable feature of the ACA, and therefore because the mandate was repealed as part of the Tax Cuts and Jobs Act, the remaining provisions of the ACA are invalid as well. The Trump Administration and the Centers for Medicare & Medicaid Services, or CMS, have both stated that the ruling will have no immediate effect, and on December 30, 2018 the same judge issued an order staying the judgment pending appeal. It is unclear how this decision and any subsequent appeals and other efforts to repeal and replace the ACA will impact the ACA and our business. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results.

Furthermore, since January 2017 President Trump has signed two Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. The second Executive Order terminates the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. The loss of the cost share reduction payments is expected to increase premiums on certain policies issued by qualified health plans under the ACA. Further, on June 14, 2018, U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in ACA risk corridor payments to third-party payors who argued were owed to them. The effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business, are not yet known.

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

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

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

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

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

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

Governments outside the United States tend to impose strict price controls, which may adversely affect our revenues, if any.

In some countries, such as the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. 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, or any future collaborators, may be required to conduct a clinical trial that compares the cost-effectiveness of our product 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 business could be harmed.

We may be subject to certain healthcare laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm, fines, disgorgement, exclusion from participation in government healthcare programs, curtailment or restricting of our operations, and diminished profits and future earnings.

Healthcare providers, third-party payors and others will play a primary role in the recommendation and prescription of any products for which we obtain marketing approval. Our future arrangements with healthcare providers and third-party payors will 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 products for which we obtain marketing approval. Potentially applicable U.S. federal and state healthcare laws and regulations include the following:

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

False Claims Laws. The federal false claims laws, including the civil False Claims Act, impose criminal and civil penalties, including those from civil whistleblower or *qui tam* actions against individuals or entities for knowingly presenting, or causing to be presented to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;

HIPAA. The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing or attempting to execute a scheme to defraud any healthcare benefit program;

HIPAA and HITECH. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or the HITECH Act, also imposes obligations on certain types of individuals and entities, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;

False Statements Statute. The federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;

Transparency Requirements. The federal Physician Payments Sunshine Act requires certain manufacturers of drugs, devices, biologics, and medical supplies for which payment is available under Medicare, Medicaid, or the Children's Health Insurance Program, with specific exceptions, to report annually to the U.S. Department of Health and Human Services information related to physician payments and other transfers of value and physician ownership and investment interests; and

Analogous State and Foreign Laws. Analogous state laws and regulations, such as state anti-kickback and false claims laws, and transparency laws, may apply to sales or marketing arrangements, and claims involving healthcare items or services reimbursed by non-governmental third party payors, including private insurers, and some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, in addition to requiring drug manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures. Many state 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. Foreign laws also govern the privacy and security of health information in many circumstances.

Efforts to ensure that our business arrangements with third parties, and our business generally, 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, disgorgement, contractual damages, and reputational harm, any of which could substantially disrupt our operations. If any of the physicians or other providers or entities with whom we expect to do business is found not to be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

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

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

We have adopted a Code of Business Conduct and Ethics that mandates compliance with the FCPA and other anti-corruption laws applicable to our business throughout the world. We cannot assure you, however, that our employees and third party intermediaries will comply with this code or such anti-corruption laws. 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.

We are subject to governmental export and import controls that could impair our ability to compete in international markets due to licensing requirements and subject us to liability if we are not in compliance with applicable laws.

Our products and solutions are subject to export control and import laws and regulations, including the U.S. Export Administration Regulations, U.S. Customs regulations, and various economic and trade sanctions regulations administered by the U.S. Treasury Department's Office of Foreign Assets Controls. Exports of our products and solutions outside of the United States must be made in compliance with these laws and regulations. If we fail to comply with these laws and regulations, we and certain of our employees could be subject to substantial civil or criminal penalties, including the possible loss of export or import privileges; fines, which may be imposed on us and responsible employees or managers; and, in extreme cases, the incarceration of responsible employees or managers.

In addition, changes in our products or solutions or changes in applicable export or import laws and regulations may create delays in the introduction, provision, or sale of our products and solutions in international markets, prevent customers from using our products and solutions or, in some cases, prevent the export or import of our products and solutions to certain countries, governments or persons altogether. Any limitation on our ability to export, provide, or sell our products and solutions could adversely affect our business, financial condition and results of operations.

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 harm 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. From time to time and in the future, our operations may involve the use of hazardous and flammable materials, including chemicals and biological materials, and may also produce hazardous waste products. Even if we contract with third parties for the disposal of these materials and waste products, we cannot completely eliminate the risk of contamination or injury resulting from these materials. In the event of contamination or injury resulting from the use or disposal of our 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 for failure to comply with such laws and regulations.

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, but this insurance may not provide adequate coverage against potential liabilities. We do not, however, maintain insurance for environmental liability or toxic tort claims that may be asserted against us.

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

Unfavorable global economic conditions could adversely affect our business, financial condition or results of operations.

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. The most recent global financial crisis caused extreme volatility and disruptions in the capital and credit markets, and it is unclear what impact the decision by the United Kingdom to leave the European Union will have on the global economy. A severe or prolonged economic downturn, such as the most recent global financial crisis, could result in a variety of risks to our business, including weakened demand for our product candidates and our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could strain our suppliers, possibly resulting in supply disruption, or cause delays in payments for our services by third-party payors or our collaborators. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

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

Despite the implementation of security measures and certain data recovery measures, our internal computer systems and those of our current and any future collaborators and other contractors or consultants are vulnerable to damage from cyber-attacks, computer viruses, unauthorized access, sabotage, natural disasters, terrorism, war and telecommunication and electrical failures. Any system failure, accident or security breach that causes interruptions in our operations, for us or those third parties with which we contract, could result in a material disruption of our product development programs and our 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 clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we may incur liabilities, our competitive position could be harmed and the further development and commercialization of our product candidates may be delayed. In addition, we may not have adequate insurance coverage to provide compensation for any losses associated with such events.

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. In addition, outside parties may attempt to penetrate our systems or those of our vendors or fraudulently induce our employees or employees of our vendors to disclose sensitive information to gain access to our data. Like other companies, we may experience threats to our data and systems, including malicious codes and viruses, and other cyber-attacks. The number and complexity of these threats continue to increase over time. 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.

Our employees may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements, which could cause significant liability for us and harm our reputation.

We are exposed to the risk of employee fraud or other misconduct, including intentional failures to comply with FDA regulations or similar regulations of comparable foreign regulatory authorities, provide accurate information to the FDA or comparable foreign regulatory authorities, comply with manufacturing standards we have established, comply with federal and state healthcare fraud and abuse laws and regulations and similar laws and regulations established and enforced by comparable foreign regulatory authorities, report financial information or data accurately or disclose unauthorized activities to us. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. 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, standards 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.

Risks Related to Employee Matters and Managing Growth

Our future success depends on our ability to retain our executive officers and to attract, retain and motivate qualified personnel.

We are highly dependent on the pharmaceutical research and development and business development expertise of Nancy Simonian, M.D., our president and chief executive officer; Joseph J. Ferra, Jr., our chief financial officer; Eric R. Olson, Ph.D., our chief scientific officer; Gerald E. Quirk, Esq., our chief legal and administrative officer; David A. Roth, M.D., our chief medical officer; and Jeremy P. Springhorn, Ph.D., our chief business officer. Each of our executive officers is employed "at will," meaning any of them may terminate his or her employment with us at any time with or without notice and for any reason or no reason.

Our ability to compete in the biotechnology and pharmaceuticals industries depends upon our ability to attract and retain highly qualified managerial, scientific and medical personnel. Our industry has experienced a high rate of turnover of management personnel in recent years. If we lose one or more of our executive officers or other key employees, our ability to implement our business strategy successfully could be seriously harmed. Replacing executive officers or other key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to develop, gain marketing approval of and commercialize products successfully. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these additional key employees on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions.

We rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by other entities and may have commitments under consulting or advisory contracts with those entities that may limit their availability to us. If we are unable to continue to attract and retain highly qualified personnel, our ability to develop and commercialize our product candidates will be limited.

We expect to expand our organization, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of clinical development, drug manufacturing, regulatory affairs and sales, marketing and distribution. To manage these growth activities, 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. Our management may need to devote a significant amount of its attention to managing these growth activities. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion or relocation of our operations, retain key employees, or identify, recruit and train additional qualified personnel. Our inability to manage the expansion or relocation of our operations effectively may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could also require significant capital expenditures and may divert financial resources from other projects, such as the development of additional product candidates. If we are unable to effectively manage our expected growth, our expenses may increase more than expected, our ability to generate revenues could be reduced and we may not be able to implement our business strategy, including the successful commercialization of our product candidates.

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

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

Our shares of common stock began trading on the Nasdaq Global Select Market on June 30, 2016. Given the limited trading history of our common stock, there is a risk that an active trading market for our shares will not be sustained, which could put downward pressure on the market price of our common stock and thereby affect the ability of our stockholders to sell their shares. An inactive trading market may also impair our ability to raise capital to continue to fund operations by selling shares and may impair our ability to acquire other companies or technologies by using our shares as consideration.

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

Our stock price is likely to be highly volatile. The stock market in general and the market for smaller pharmaceutical and biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, you may lose some or all of your investment. The market price for our common stock may be influenced by many factors, including:

- the timing and results of clinical trials of SY-1425 and SY-5609;
- the success of existing or new competitive products or technologies;

- 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;
- commencement or termination of collaborations for our research or 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 or recommendations by securities analysts;
- announcement or expectation of additional financing efforts;
- sales of our common stock by us, our insiders or other stockholders;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in estimates or recommendations by securities analysts, if any, that cover our stock;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, industry and market conditions;
- actual or threatened public health emergencies and outbreaks of disease (including, for example, the recent coronavirus outbreak); and
- the other factors described in this "Risk Factors" section and elsewhere in our Annual Report on Form 10-K for the fiscal year ended December 31, 2019.

In the past, companies that have experienced volatility in the market price of their stock have been subject to an increased incidence of securities class action litigation. This risk is especially relevant for us because pharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

We are an "emerging growth company" and a "smaller reporting company," and the reduced disclosure requirements applicable to emerging growth companies and smaller reporting companies may make our common stock less attractive to investors.

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and may remain an emerging growth company for up to five years from the date of our initial public offering. For so long as we remain an emerging growth company, we are permitted and plan to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, or SOX Section 404, not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements, reduced disclosure obligations regarding executive compensation and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

We are also a smaller reporting company, and we will remain a smaller reporting company until the fiscal year following the determination that our voting and non-voting common shares held by non-affiliates is more than $250 million measured on the last business day of our second fiscal quarter, or our annual revenues are more than $100 million during the most recently completed fiscal year and our voting and non-voting common shares held by non-affiliates is more than $700 million measured on the last business day of our second fiscal quarter. Similar to emerging growth companies, smaller reporting companies are able to provide simplified executive compensation disclosure, are exempt from the auditor attestation requirements of Section 404, and have certain other reduced disclosure obligations, including, among other things, being required to provide only two years of audited financial statements and not being required to provide selected financial data, supplemental financial information or risk factors.

We have elected to take advantage of certain of the reduced reporting obligations. We cannot predict whether investors will find our common stock less attractive if we rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile.

We must maintain effective internal control over financial reporting, and if we are unable to do so, the accuracy and timeliness of our financial reporting may be adversely affected, which could have a material adverse effect on our business and stock price.

We must maintain effective internal control over financial reporting in order to accurately and timely report our results of operations and financial condition. In addition, as a public company, the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, requires, among other things, that we assess the effectiveness of our disclosure controls and procedures quarterly and the effectiveness of our internal control over financial reporting at the end of each fiscal year.

The rules governing the standards that must be met for our management to assess our internal control over financial reporting pursuant to Section 404 of the Sarbanes-Oxley Act are complex and require significant documentation, testing and possible remediation. These standards require that our audit committee be advised and regularly updated on management’s review of internal control over financial reporting. Our management may not be able to effectively and timely implement controls and procedures that comply with the increased regulatory compliance and reporting requirements that are applicable to us as a public company. If we fail to staff our accounting and finance function adequately or maintain internal control over financial reporting adequate to meet the demands that are placed upon us as a public company, including the requirements of the Sarbanes-Oxley Act, our business and reputation may be harmed and our stock price may decline.

We might not be able to utilize a significant portion of our net operating loss carryforwards and research and development tax credit carryforwards.

As of December 31, 2019, we had federal and state net operating loss carryforwards of $248.2 million and $251.7 million, respectively, and federal and state research and development tax credit carryforwards of $11.9 million and $2.9 million, respectively. Our net operating loss carryforwards generated prior to 2018 will generally expire at various dates through 2037. These carryforwards could expire unused and be unavailable to offset future income tax liabilities. Under the Tax Cuts and Jobs Act of 2017, federal net operating losses generated after 2017 have an indefinite carryover period, but the deductibility of such federal net operating losses is limited. In addition, under Section 382 of the Internal Revenue Code of 1986, as amended, and corresponding provisions of state law, if a corporation undergoes an "ownership change," which is generally defined as a greater than 50% change, by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change income may be limited. We have not determined if we have experienced Section 382 ownership changes in the past and if a portion of our net operating loss and tax credit carryforwards are subject to an annual limitation under Section 382. In addition, we may experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. If we determine that an ownership change has occurred and our ability to use our historical net operating loss and tax credit carryforwards is materially limited, or if our research and development carryforwards are adjusted, it would harm our future operating results by effectively increasing our future tax obligations.

We do not anticipate paying any cash dividends on our capital stock in the foreseeable future. Accordingly, stockholders must rely on capital appreciation, if any, for any return on their investment.

We have never declared nor paid cash dividends on our capital stock. We currently plan to retain all of our future earnings, if any, to finance the operation, development and growth of our business. In addition, the terms of our term loan facility with Oxford precludes us from paying cash dividends to our stockholders without Oxford's consent. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future.

Concentration of ownership of our common stock among our existing executive officers, directors and principal stockholders may prevent new investors from influencing significant corporate decisions.

Our executive officers and directors, combined with our stockholders who own more than 5% of our outstanding common stock and their affiliates, in the aggregate, beneficially own a majority of our common stock. As a result, if these stockholders were to choose to act together, they would be able to control all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would control the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of ownership control may:

- delay, defer or prevent a change in control;
- entrench our management or the board of directors; or
- impede a merger, consolidation, takeover or other business combination involving us that other stockholders may desire.

Provisions in our certificate of incorporation and bylaws and under Delaware law may prevent or frustrate attempts by our stockholders to change our management or hinder efforts to acquire a controlling interest in us.

Provisions in our certificate of incorporation 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 all members of the board are not 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 nominations for election to the board of directors or for proposing matters that can be acted on at stockholder meetings;
- 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 a special meeting of stockholders;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a "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 certificate of incorporation or bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the General Corporation Law of the State of Delaware, 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. This could discourage, delay or prevent someone from acquiring us or merging with us, whether or not it is desired by, or beneficial to, our stockholders. This could also have the effect of discouraging others from making tender offers for our common stock, including transactions that may be in your best interests. These provisions may also prevent changes in our management or limit the price that investors are willing to pay for our stock.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our share price and trading volume could decline.

The trading market for our common stock will likely depend in part on the research and reports that securities or industry analysts publish about us or our business. We do not have any control over these analysts. There can be no assurance that analysts will cover us, or provide favorable coverage. Securities or industry analysts may elect not to provide research coverage of our common stock, and such lack of research coverage may negatively impact the market price of our common stock. In the event we do have analyst coverage, if one or more analysts downgrade our stock or change their opinion of our stock, our share price would likely decline. In addition, if one or more analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our share price or trading volume to decline.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

We currently occupy approximately 52,859 rentable square feet of office and laboratory space in Cambridge, Massachusetts under a lease that expires in February 2030. We have an option to extend the lease term for 10 additional years. We believe that our office and laboratory space is sufficient to meet our current needs and that suitable additional space will be available as and when needed.

ITEM 3. LEGAL PROCEEDINGS

None.

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

Certain Information Regarding the Trading of Our Common Stock

Our common stock trades under the symbol "SYRS" on the Nasdaq Global Select Market and has been publicly traded since June 30, 2016. Prior to this time, there was no public market for our common stock.

Holders of Our Common Stock

As of February 29, 2020, there were approximately 34 holders of record of shares of our common stock. This number does not include stockholders for whom shares are held in "nominee" or "street" name.

ITEM 6. SELECTED CONSOLIDATED FINANCIAL DATA

The following selected consolidated financial data should be read together with our financial statements and the related notes appearing at the end of this Annual Report on Form 10-K and Part II, Item 7 "Management's Discussion and Analysis of Financial Condition and Results of Operations" of this Annual Report on Form 10-K. We have derived the consolidated statement of operations data for the years ended December 31, 2019, 2018 and 2017 and the consolidated balance sheet data as of December 31, 2019 and 2018 from our audited consolidated financial statements included elsewhere in this Annual Report on Form 10-K. We derived the selected consolidated financial data for the years ended December 31, 2016 and 2015 and as of December 31, 2017, 2016 and 2015 from audited financial statements that are not included in this Annual Report on Form 10-K. The selected historical financial information in this section is not intended to replace our financial statements and the related notes thereto. Our historical results for any prior period are not necessarily indicative of results to be expected in any future period.

	Year ended December 31,				
	2019	2018	2017	2016	2015
	(in thousands, except for share per share data)				
Statements of operations data:					
Revenue	$ 1,982	$ 2,050	$ 1,101	$ 317	$ 317
Operating expenses:					
Research and development	58,245	50,182	41,896	37,817	24,408
General and administrative	21,478	16,164	13,891	10,463	5,729
Total operating expenses	79,723	66,346	55,787	48,280	30,137
Loss from operations	(77,741)	(64,296)	(54,686)	(47,963)	(29,820)
Other income, net	2,303	2,017	676	220	2
Net loss	$ (75,438)	$ (62,279)	$ (54,010)	$ (47,743)	$ (29,818)
Accrued dividends on preferred stock	—	—	—	(3,681)	$ (4,934)
Net loss applicable to common shareholders	$ (75,438)	$ (62,279)	$ (54,010)	$ (51,424)	$ (34,752)
Net loss per share applicable to common stockholders - basic and diluted (1)	$ (1.88)	$ (1.91)	$ (2.13)	$ (4.05)	$ (17.55)
Weighted-average number of common shares used in net loss per share applicable to common stockholders - basic and diluted (1)	40,222,182	32,656,237	25,406,845	12,696,414	1,980,286

	As of December 31,			
	2019	2018	2017	2016
	(in thousands)			
Balance sheet data:				
Cash, cash equivalents and marketable securities	$ 91,416	$ 99,679	$ 72,049	$ 83,593
Working capital (2)	90,997	82,205	60,746	75,941
Total assets	149,978	106,766	78,488	91,323
Total stockholders' equity	79,184	78,586	65,324	80,602

(1) See Note 2 to our consolidated financial statements in Part II of this Annual Report on Form 10-K for a description of the method used to calculate basic and diluted net loss per share as well as the weighted-average number of common shares used in the calculation of the per share amounts.

(2) We define working capital as current assets less current liabilities. See our consolidated financial statements in Part II of this Annual Report on Form 10-K for further details regarding our current assets and current liabilities.

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

The following discussion and analysis of our financial condition and results of operations should be read in conjunction with our audited financial statements and related notes appearing elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis and set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. You should review the section titled "Risk Factors" in Part I, Item 1A of this Annual Report 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 seeking to redefine the power of small molecules to control the expression of genes. Based on our unique ability to elucidate regulatory regions of the genome, we aim to develop medicines that provide a profound benefit for patients with diseases that have eluded other genomics-based approaches. We are currently focused on developing treatments for cancer and diseases resulting from mutations of a single gene, also known as monogenic diseases, and building a pipeline of gene control medicines.

Our lead product candidates are:

- SY-1425, a selective retinoic acid receptor alpha, or RARα, agonist that is currently being evaluated in combination with azacitidine, a hypomethylating agent frequently used to treat acute myeloid leukemia, or AML, patients in a Phase 2 clinical trial in a genomically defined subset of patients with AML; and

- SY-5609, a highly selective and potent oral inhibitor of cyclin-dependent kinase 7, or CDK7, that is currently being evaluated in the dose escalation portion of a Phase 1 clinical trial in patients with select advanced solid tumors.

In October 2019, we announced a decision to prioritize the development of SY-5609 and to discontinue further development of SY-1365, our intravenously administered CDK7 inhibitor for which we are conducting a Phase 1 clinical trial in patients with advanced solid tumors.

We also have multiple preclinical and discovery programs in oncology and monogenic diseases such as sickle cell disease and myotonic dystrophy type 1. We expect to nominate our next development candidate to enter investigational new drug application, or IND, enabling preclinical studies by the end of 2021. In December 2019, we entered into a collaboration with Global Blood Therapeutics, Inc., or GBT, to discover, develop and commercialize novel therapies for sickle cell disease and beta thalassemia. We also use our gene control platform in collaboration with third parties to identify and validate targets in diseases beyond our current areas of focus. To this end, we entered into a target discovery, research collaboration and option agreement with Incyte Corporation, or Incyte, in January 2018 under which we are using our platform to identify novel therapeutic targets with a focus on myeloproliferative neoplasms.

Our ongoing Phase 2 clinical trial is assessing the safety and efficacy of SY-1425 in combination with azacitidine in approximately 25 newly diagnosed AML patients who are "unfit," meaning that they are not suitable candidates for standard intensive chemotherapy, who have been prospectively selected using our proprietary RARA or IRF8 biomarkers, as well as in approximately 25 newly diagnosed unfit AML patients who are biomarker-negative. The biomarker-negative patients are being enrolled to support the development of a commercial companion diagnostic test for SY-1425. In addition, we are evaluating the safety and efficacy of SY-1425 in combination with azacitidine in approximately 25 relapsed or refractory AML patients who are being prospectively selected using the RARA biomarker.

At the European School of Haemotology International Conference on AML held in October 2019, or ESH 2019, we reported data from the newly diagnosed unfit AML cohorts of the Phase 2 clinical trial as of an August 22, 2019 data cut-off. Enrollment in the newly diagnosed unfit AML cohorts of the trial is complete and we continue to follow patients in the trial. As of the data cut-off, 40 newly diagnosed unfit AML patients had been enrolled in the trial and were eligible for the safety analysis. We reported at ESH 2019 that SY-1425 in combination with azacitidine had been generally well-tolerated, with no evidence of increased toxicities due to the combination, and that adverse events had been consistent with what has previously been seen with SY-1425 and azacitidine as single agents in AML. Across all grades and causalities, the most commonly reported adverse events in these cohorts of the trial were nausea, decreased appetite, constipation, fatigue and peripheral edema, the majority of which were low grade. Of the 17 biomarker-positive patients evaluable for response, 13 were RARA-positive and four were IRF8-positive. We reported at ESH 2019 that the aggregate rate of complete response, or CR, and

complete response with incomplete blood count recovery, or CRi, in each case as defined by Revised International Working Group, or IWG, criteria for AML, as of the data cut-off in RARA-positive patients was 62% and the CR rate was 54%. The duration of responses in RARA-positive patients was up to 344 days, with three of the eight responding patients having responses lasting beyond seven months at the time of the data cut-off. In patients with only the IRF8 biomarker, the CR/CRi rate was 0%, supporting our decision to use RARA as the sole biomarker for patient selection in SY-1425 clinical trials going forward. Most of the initial responses reported were seen at the end of the first treatment cycle. In 22 response-evaluable RARA-negative patients, the CR/CRi rate was 27%. Single-agent azacitidine has shown response rates of 18-29% in newly diagnosed unfit AML patients, with initial responses generally occurring after four cycles of treatment in most patients who respond. We expect to report mature data from the newly diagnosed AML cohorts of the trial, as well as potential proof-of-concept data from the relapsed or refractory AML cohort of the trial, in the fourth quarter of 2020.

In January 2020, we dosed the first patient in a Phase 1 clinical trial of SY-5609 in patients with select advanced solid tumors, including breast, colorectal, lung and ovarian cancers, and in solid tumors of any histology having retinoblastoma-pathway, or Rb pathway, alterations. The primary objectives of this trial are to assess the safety and tolerability of escalating doses of SY-5609, with the goal of establishing a maximum tolerated dose. Additional objectives include assessments of anti-tumor activity, pharmacokinetics, pharmacodynamics and potential predictive biomarkers, including Rb pathway alterations. In a future expansion portion of the Phase 1 trial, multiple cohorts are planned to further evaluate the safety and anti-tumor activity of SY-5609 as both a single agent and in combination with other therapies. We expect to report initial safety, tolerability, and pharmacokinetic and pharmacodynamic data from the trial in the fourth quarter of 2020. We also expect to report additional dose escalation data, including clinical activity data, in mid-2021.

At the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics held in October 2019, or ENA 2019, we presented preclinical data characterizing the profile of SY-5609. These data show that SY-5609 is a potent and highly selective CDK7 inhibitor, with at least 13,000-fold greater selectivity for CDK7 over closely related members of the cyclin- dependent kinase family. In addition, we reported at ENA 2019 that SY-5609 induced dose-dependent tumor growth inhibition in preclinical models of ovarian and breast cancer, tumor regressions that were sustained after the end of treatment at well-tolerated doses in multiple preclinical models of triple-negative breast, small cell lung, and high-grade serous ovarian cancers. Deeper and more sustained responses in these models were associated with the presence of Rb pathway alterations. We also reported preclinical data showing the anti-tumor activity of SY-5609 in combination with fulvestrant, a hormonal therapy, in treatment-resistant preclinical models of estrogen receptor-positive breast cancer. We have shown that SY-5609 inhibits CDK7 more potently and selectively than SY-1365, and that SY-5609 demonstrated greater tumor growth inhibition than SY-1365 in preclinical models in which both agents were studied, including models that were not responsive to SY-1365.

In October 2019, we announced data from the expansion portion of our Phase 1 clinical trial evaluating SY-1365 in multiple solid tumor indications. As of a September 30, 2019 data snapshot, 68 patients had been treated in the expansion portion of this trial, including 53 across the single-agent cohorts in patients with high-grade serous ovarian cancer, relapsed clear cell ovarian cancer, and solid tumors of any histology available for biopsy, and 15 patients in combination cohorts evaluating SY-1365 in combination with carboplatin, a chemotherapeutic agent, in patients with high-grade serous ovarian cancer and in combination with fulvestrant in patients with treatment-resistant metastatic hormone-receptor positive breast cancer. We initiated the single-agent expansion cohorts at a dose of 80 mg/m^2 twice weekly and the combination cohorts at 53 mg/m^2 once weekly after having observed data from the dose-escalation portion of the trial demonstrating dose-dependent effects on CDK7 occupancy and downstream gene expression changes in blood cells as well as a confirmed partial response in one patient with recurrent clear cell ovarian cancer. During the expansion portion of the trial, adverse events occurring around the time of infusion of SY-1365, which we believe to be related to the intravenous administration of SY-1365, prompted us to evaluate lower doses in the single-agent cohorts and extended infusion times across all of the cohorts. We refer to adverse events occurring around the time of infusion as peri-infusional adverse events. Extended infusion times reduced peak drug concentrations while maintaining CDK7 target occupancy and appeared to reduce the overall frequency and severity of these peri-infusional adverse events, including headache, nausea and vomiting. The best response observed across the expansion cohorts of the trial was stable disease, as defined by Response Evaluation Criteria in Solid Tumors criteria. Of the 31 response-evaluable patients treated with SY-1365 as a single agent, 13 of them, or 42%, had stable disease. Of the 11 response-evaluable patients treated in the combination cohorts of the trial, seven of them, or 64%, had stable disease. Based on preclinical and clinical data generated to date, we believe that sustaining the level of CDK7 target coverage needed to enhance clinical activity with SY-1365 would require more frequent dosing, or a higher dose that would necessitate lengthening the infusion time to manage tolerability. We believe that either approach could create an overly burdensome dosing regimen for patients that could be better addressed with an oral agent like SY-5609. This belief, coupled with the superior preclinical data generated with SY-5609 relative to SY-1365 and a competitive landscape in oncology increasingly focused on oral agents, led us to make a portfolio decision to discontinue further development of SY-1365 and prioritize the development of SY-5609.

Recent Developments

In February 2020, we into a Loan and Security Agreement, or Loan Agreement, with Oxford Finance LLC, or Oxford, pursuant to which a term loan of up to an aggregate principal amount of $60.0 million was made available to us. A $20.0 million term loan was funded at closing, and two additional term loan advances of $20.0 million each will be available under the Loan Agreement after the closing date, subject to certain terms and conditions, including the achievement of certain milestones. In connection with entry into the Loan Agreement, we issued Oxford warrants to purchase 27,548 shares of our common stock at an exercise price per share of $7.26. These warrants will be exercisable for five years from the date of issuance.

The term loans bear interest at an annual rate equal to the greater of (i) 7.75% and (ii) the sum of 5.98% and the greater of (A) one-month LIBOR and (B) 1.77%. The Loan Agreement provides for interest-only payments until March 1, 2023, and repayment of the aggregate outstanding principal balance of the term loan in monthly installments starting on March 1, 2023 and continuing through February 1, 2025. We paid a facility fee of $100,000 at closing and are obligated to pay a facility fees upon the closing of the subsequent tranches. We may elect to prepay the loans subject to the payment of a prepayment fee. In connection with the Loan Agreement, we granted Oxford a security interest in all of our personal property now owned or hereafter acquired, excluding intellectual property (but including the right to payments and proceeds of intellectual property), and a negative pledge on intellectual property. The Loan Agreement also contains certain events of default, representations, warranties and non-financial covenants.

Financial Operations Overview

Revenue

To date, we have not generated any revenue from product sales and do not expect to generate any revenue from product sales for the foreseeable future. For the years ended December 31, 2019 and 2018, we recognized approximately $2.0 million and $2.1 million of revenue, respectively, all of which is attributable to our collaboration agreement with Incyte. For the year ended December 31, 2017, we recognized $1.1 million of revenue, all of which was attributable to a research agreement with a multinational pharmaceutical company that expired in March 2017 in accordance with its terms.

Expenses

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for our research activities, including development of our gene control platform and the development of product candidates, which include:

- employee-related expenses, including salaries and benefits;
- stock-based compensation expense;
- external costs of funding activities performed by third parties that conduct research and development on our behalf and of purchasing supplies used in designing, developing and manufacturing preclinical study and clinical trial materials;
- consulting, licensing and professional fees related to research and development activities; and
- facilities costs, depreciation and amortization and other expenses, which include direct and allocated expenses for rent and maintenance of facilities, insurance and other operating costs.

Research and development costs are expensed as incurred. Nonrefundable advance payments made to vendors for goods or services that will be received in the future for use in research and development activities are deferred and capitalized, even when there is no alternative future use for the research and development, until related goods or services are provided.

We typically use our employee, consultant and infrastructure resources across our research and development programs. We track outsourced development costs by product candidate or development program, but we do not allocate personnel costs, other internal costs or certain external consultant costs to specific product candidates or development programs.

The following table summarizes our external research and development expenses by program, as well as expenses not allocated to programs, for the years ended December 31, 2019, 2018 and 2017 (in thousands):

	Year Ended December 31,		
	2019	2018	2017
SY-1425 external costs (1)	$ 7,076	$ 6,901	$ 9,227
SY-5609 and other CDK7 program external costs (1)	15,992	18,234	8,289
Other research and platform program external costs	10,580	6,971	8,161
Employee-related expenses, including stock-based compensation	19,034	13,957	11,719
Facilities and other expenses	5,563	4,119	4,500
Total research and development expenses	$ 58,245	$ 50,182	$ 41,896

(1) The results for the year ended December 31, 2019 include credits of $1.9 million and $1.2 million for our SY-1425 and SY-1365 clinical trials, respectively, due to a change in estimate of costs incurred over the life of these clinical trials through March 31, 2019.

We expect our research and development expenses will increase for the foreseeable future as we seek to advance our programs. 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 development of our product candidates. We are also unable to predict when, if ever, material net cash inflows will commence from sales of our product candidates. This is due to the numerous risks and uncertainties associated with developing such product candidates, including the uncertainty of:

- successful completion of preclinical studies, including activities related to preparation of INDs and minimally efficacious dose studies in animals, where applicable and required, under the requirements of the U.S. Food and Drug Administration, or FDA, or another regulatory authority;
- approval of INDs for our product candidates to commence planned or future clinical trials;
- successful enrollment in, and completion of, clinical trials;
- successful data from our clinical programs that support an acceptable benefit-risk profile of our product candidates in the intended populations;
- successful development, and subsequent clearance or approval, of companion diagnostic tests for use in identifying potential patients;
- receipt of regulatory approvals from applicable regulatory authorities;
- establishment of arrangements with third-party manufacturers for clinical supply and commercial manufacturing and, where applicable, commercial manufacturing capabilities;
- establishment and maintenance of patent and trade secret protection or regulatory exclusivity for our product candidates;
- commercial launch of our product candidates, if and when approved, whether alone or in collaboration with others;
- enforcement and defense of intellectual property rights and claims;
- maintenance of a continued acceptable safety profile of the product candidates following approval; and
- retention of key research and development personnel.

Any changes in the outcome of any of these variables with respect to the development of our product candidates in preclinical and clinical development could mean a significant change in the costs and timing associated with the development of these product candidates. For example, if the FDA or another regulatory authority were to delay our planned start of clinical trials or require us to conduct clinical trials or other testing beyond those that we currently expect or if we experience significant delays in enrollment in any of our planned clinical trials, we could be required to expend significant additional financial resources and time on the completion of clinical development of our product candidates.

General and Administrative Expenses

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

We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support our continued research activities and development of our product candidates.

Other Income, Net

Other income, net, consists of interest income on our cash and cash equivalents, interest, and amortization of premiums and discounts on our investments in marketable securities, net of interest expense related to our equipment financing arrangements.

Critical Accounting Policies and Estimates

Our management's discussion and analysis of our financial condition and results of operations are based on our financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles, or U.S. GAAP. The preparation of these financial statements requires us to make judgments and estimates that affect the reported amounts of assets, liabilities, revenues and expenses and the disclosure of contingent assets and liabilities in our financial statements. We base our estimates on historical experience, known trends and events and various other factors that are believed to be reasonable under the circumstances. Actual results may differ from these estimates under different assumptions or conditions. On an ongoing basis, we evaluate our judgments and estimates in light of changes in circumstances, facts and experience. The effects of material revisions in estimates, if any, will be reflected in the financial statements prospectively from the date of the change in estimates.

While our significant accounting policies are described in more detail in the notes to our financial statements appearing elsewhere in this report, we believe the following accounting policies used in the preparation of our financial statements require the most significant judgments and estimates.

Revenue

To date our only revenue has consisted of collaboration and license revenue. We have not generated any revenue from product sales and do not expect to generate any revenue from product sales for the foreseeable future. For the years ended December 31, 2019 and 2018, we recognized approximately $2.0 million and $2.1 million of revenue, respectively, all of which was attributable to our target discovery collaboration with Incyte. For the year ended December 31, 2017, we recognized $1.1 million of revenue, all of which was attributable to a research agreement with a multinational pharmaceutical company that expired in accordance with its terms in March 2017.

On January 1, 2018, we adopted Accounting Standards Codification, or ASC 606, *Revenue from Contracts with Customers* ("ASC 606"). ASC 606 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. Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs 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) the entity satisfies a performance obligation.

We only apply the five-step model to contracts when it is probable that we will collect the consideration to which we are entitled 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 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.

From time to time, we may enter into agreements that are within the scope of ASC 606. The terms of these arrangements typically include payment to us of one or more of the following: non-refundable, up-front license fees, prepaid research and development services, development, regulatory and commercial milestone payments; and royalties on net sales of licensed products. Each of these payments would result in license and collaboration revenues, except for revenues from royalties on net sales of licensed products, which will be classified as royalty revenues.

We analyze our collaboration arrangements to assess whether they are within the scope of ASC 808, *Collaborative Arrangements* ("ASC 808"), to determine whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities. This assessment is performed throughout the life of the arrangement based on changes in the responsibilities of all parties in the arrangement. For collaboration arrangements within the scope of ASC 808 that contain multiple elements, we first determine which elements of the collaboration are deemed to be within the scope of ASC 808 and those that are more reflective of a vendor-customer relationship and therefore within the scope of ASC 606. For elements of collaboration arrangements that are accounted for pursuant to ASC 808, an appropriate recognition method is determined and applied consistently, generally by analogy to ASC 606. For those elements of the arrangement that are accounted for pursuant to ASC 606, we apply the five-step model described above.

Research and Development Expenses

Expenditures relating to research and development are expensed in the period incurred. Research and development expenses consist of both internal and external costs associated with the development of our gene control platform and product candidates. Research and development costs include salaries and benefits, materials and supplies, external research, preclinical and clinical development expenses, stock-based compensation expense and facilities costs. Facilities costs primarily include the allocation of rent, utilities, depreciation and amortization.

In certain circumstances, we are required to make nonrefundable advance payments to vendors for goods or services that will be received in the future for use in research and development activities. In such circumstances, the nonrefundable advance payments are deferred and capitalized, even when there is no alternative future use for the research and development, until related goods or services are provided.

We record accruals for estimated ongoing research costs. When evaluating the adequacy of the accrued liabilities, we analyze progress of the work being performed, including the phase or completion of the event, invoices received and costs. Significant judgements and estimates may be made in determining the accrued balances at the end of any reporting period. Actual results could differ from our estimates.

We may in-license the rights to develop and commercialize product candidates. For each in-license transaction, we evaluate whether we have acquired processes or activities along with inputs that would be sufficient to constitute a "business" as defined under U.S. GAAP. A "business" as defined under U.S. GAAP consists of inputs and processes applied to those inputs that have the ability to create outputs. Although businesses usually have outputs, outputs are not required for an integrated set of activities to qualify as a business. When we determine that we have not acquired sufficient processes or activities to constitute a business, any up-front payments, as well as milestone payments, are immediately expensed as acquired research and development in the period in which they are incurred.

Stock-Based Compensation

We account for our stock-based compensation awards in accordance with ASC 718, *Compensation—Stock Compensation* ("ASC 718"). ASC 718 requires all stock-based payments to employees and directors, including grants of restricted stock units and stock option awards, to be recognized as expense in the consolidated statements of operations based on their grant date fair values. Effective January 1, 2019, grants of restricted stock units and stock option awards to other service providers, referred to as non-employees, are measured based on the grant-date fair value of the award and expensed in our consolidated statement of operations over the vesting period. Through December 31, 2018, grants of restricted stock unit and stock option awards to non-employees were required to be recognized as expense in the consolidated statements of operations based on their vesting date fair values. We estimate the fair value of stock options granted using the Black-Scholes option-pricing model. Prior to June 30, 2016, we were a private company and, therefore, lack company-specific historical and implied volatility information. As a result, we estimate our expected stock volatility based on the historical volatility of a publicly traded set of peer companies and expect to continue to do so until such time as we have adequate historical data regarding the volatility of our own traded stock price. The expected term of our stock options has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" options. Through December 31, 2018, the expected term of stock options granted to non-employees was equal to the contractual term of the option award. Effective January 1, 2019, the expected term of stock options to non-employees can be determined using either the contractual term of the option award or the "simplified" method. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. Expected dividend yield is based on the fact that we have never paid cash dividends and do not expect to pay any cash dividends in the foreseeable future. We use the value of our common stock to determine the fair value of restricted stock awards.

We expense the fair value of our stock-based awards to employees and non-employees on a straight-line basis over the associated service period, which is generally the vesting period. We account for forfeitures as they occur instead of estimating forfeitures at the time of grant. Ultimately, the actual expense recognized over the vesting period will be for only those options that vest.

Compensation expense for discounted purchases under the employee stock purchase plan is measured using the Black-Scholes model to compute the fair value of the lookback provision plus the purchase discount and is recognized as compensation expense over the offering period.

For stock-based awards that contain performance-based milestones, we record stock-based compensation expense in accordance with the accelerated attribution model. Management evaluates when the achievement of a performance-based milestone is probable based on the expected satisfaction of the performance conditions as of the reporting date. For certain of our performance-based awards, notwithstanding any vesting in accordance with the achievement of performance-based milestones, such awards vest in full on the sixth anniversary of the vesting commencement date. Compensation expense for such awards is recognized over the six-year vesting period unless management determines that the achievement of any performance-based milestones is probable, in which case expense is accelerated.

We have computed the fair value of stock options at the date of grant using the following weighted-average assumptions:

	Year Ended December 31,		
	2019	2018	2017
Weighted-average risk-free interest rate	2.42 %	2.56 %	2.07 %
Expected dividend yield	— %	— %	— %
Expected option term (in years)	6.00	6.04	6.05
Volatility	91.35 %	90.26 %	87.83 %

Results of Operations

Comparison of Years Ended December 31, 2019 and 2018

The following table summarizes our results of operations for the years ended December 31, 2019 and 2018, together with the changes in those items in dollars (in thousands):

	Year Ended December 31,			
	2019	2018	Dollar Change	% Change
Statements of Operations Data:				
Revenue	$ 1,982	$ 2,050	$ (68)	(3)%
Operating expenses:				
Research and development	58,245	50,182	8,063	16 %
General and administrative	21,478	16,164	5,314	33 %
Total operating expenses	79,723	66,346	13,377	20 %
Other income, net	2,303	2,017	286	14 %
Net loss	$ (75,438)	$ (62,279)	$ (13,159)	(21)%

Revenue

For the year ended December 31, 2019 and 2018, we recognized approximately $2.0 million and $2.1 million of revenue, all of which was attributable to our target discovery collaboration with Incyte.

Research and Development Expense

Research and development expense increased by approximately $8.0 million, or 16%, from $50.2 million for the year ended December 31, 2018 to $58.2 million for the year ended December 31, 2019. The following table summarizes our research and development expenses for the years ended December 31, 2019 and 2018, together with the changes to those items in dollars (in thousands):

	Year Ended December 31,			
	2019	2018	Dollar Change	% Change
External research and development	$ 30,129	$ 30,255	$ (126)	0%
Employee-related expenses, excluding stock-based compensation	15,561	11,545	4,016	35%
Stock-based compensation	3,472	2,412	1,060	44%
Consulting, licensing and professional fees	3,520	1,851	1,669	90%
Facilities and other expenses	5,563	4,119	1,444	35%
Total research and development expenses	$ 58,245	$ 50,182	$ 8,063	16%

The change in research and development expense was primarily attributable to research and development activities associated with advancing our lead clinical and preclinical programs and enhancing our internal capabilities, and included the following:

- an increase of approximately $4.0 million, or 35%, for increased employee-related expenses, including increased salary and benefits primarily due to our increased headcount;
- an increase of approximately $1.1 million, or 44%, for stock-based compensation, also primarily due to our increased headcount;
- an increase of approximately $1.7 million, or 90%, consulting, licensing and professional fees increased professional fees in support of our SY-1425, SY-1365 and SY-5609 clinical trials and our other preclinical programs; and
- an increase of approximately $1.4 million, or 35%, in facilities and other expenses primarily due to the rent expense related to the lease for our new headquarters, over which we took possession for accounting purposes in May 2019.

General and Administrative Expense

General and administrative expense increased by approximately $5.3 million, or 33% from $16.2 million for the year ended December 31, 2018 to $21.5 million for the year ended December 31, 2019. The change in general and administrative expense was primarily attributable to an increase in employee-related costs, including salary, benefits and stock-based compensation, primarily due to our increased headcount period over period.

Other Income, Net

Other income, net, consists of interest income on our cash and cash equivalents, interest, and amortization of premiums and discounts on marketable securities, net of interest expense related to our equipment financing arrangements. The increase in other income, net, from the year ended December 31, 2018 to the year ended December 31, 2019 is due to higher average cash balances during 2019 as compared to 2018.

Comparison of Years Ended December 31, 2018 and 2017

The following table summarizes our results of operations for the years ended December 31, 2018 and 2017, together with the changes in those items in dollars (in thousands):

	Year Ended December 31,			
	2018	2017	Dollar Change	% Change
Statements of Operations Data:				
Revenue	$ 2,050	$ 1,101	$ 949	86 %
Operating expenses:				
Research and development	50,182	41,896	8,286	20 %
General and administrative	16,164	13,891	2,273	16 %
Total operating expenses	66,346	55,787	10,559	19 %
Other income, net	2,017	676	1,341	198 %
Net loss	$ (62,279)	$ (54,010)	$ (8,269)	(15)%

Revenue

For the year ended December 31, 2018, we recognized approximately $2.1 million of revenue, all of which is attributable to our target discovery collaboration with Incyte. For the year ended December 31, 2017, we recognized $1.1 million of revenue, all of which was attributable to a research agreement with a multinational pharmaceutical company that expired in accordance with its terms in March 2017.

Research and Development Expense

Research and development expense increased by approximately $8.3 million, or 20%, from $41.9 million for the year ended December 31, 2017 to $50.2 million for the year ended December 31, 2018. The following table summarizes our research and development expenses for the years ended December 31, 2018 and 2017, together with the changes to those items in dollars (in thousands):

	Year Ended December 31,			
	2018	2017	Dollar Change	% Change
External research and development	$ 30,255	$ 23,785	$ 6,470	27 %
Employee-related expenses, excluding stock-based compensation	11,545	10,053	1,492	15 %
Stock-based compensation	2,412	1,666	746	45 %
Consulting, licensing and professional fees	1,851	1,892	(41)	(2)%
Facilities and other expenses	4,119	4,500	(381)	(8)%
Total research and development expenses	$ 50,182	$ 41,896	$ 8,286	20 %

The change in research and development expense was primarily attributable to research and development activities associated with advancing our lead clinical and preclinical programs and enhancing our internal capabilities, and included the following:

- an increase of approximately $6.5 million, or 27%, for external research and development costs, including a $7.5 million increase in contract manufacturing costs and $0.5 million increase in clinical management costs, offset by a $1.5 million decrease in external preclinical and supporting research and development costs;
- an increase of approximately $1.5 million, or 15%, for increased personnel related expenses, including increased salary and benefits primarily due to our increased headcount;
- an increase of approximately $0.7 million, or 45%, for stock-based compensation also primarily due to our increased headcount and the acceleration of certain performance-based stock options associated with entry into our target discovery collaboration with Incyte in January 2018; and
- a decrease of approximately $0.4 million, or 8%, in allocable costs for facilities, recruiting and other costs that were incurred during the year ended December 31, 2017, that did not reoccur during the year ended December 31, 2018.

General and Administrative Expense

General and administrative expense increased by approximately $2.3 million, or 16% from $13.9 million for the year ended December 31, 2017 to $16.2 million for the year ended December 31, 2018. The change in general and administrative expense was primarily attributable to an increase in employee-related costs, including salary, benefits and stock-based compensation, primarily due to our increased headcount period over period and the acceleration of certain performance-based stock options associated with entry into our target discovery collaboration with Incyte in January 2018.

Other Income, Net

Other income, net, consists of interest income on our cash and cash equivalents, interest, amortization of premiums and discounts on marketable securities, net of interest expense related to our equipment financing arrangements. The increase in other income, net, from the year ended December 31, 2017 to the year ended December 31, 2018 is due to the increased level of cash, cash equivalents and marketable securities attributable to our capital-raising activities during 2018.

Liquidity and Capital Resources

Sources of Liquidity

We funded our operations from inception through December 31, 2019 primarily through the sale of equity securities and research agreements with third parties, including our collaboration with Incyte.

On July 20, 2017, we filed a universal shelf registration statement on Form S-3 with the SEC to register for sale from time to time up to $225.0 million of common stock, preferred stock, debt securities, warrants and/or units in one or more registered offerings. The shelf registration statement was declared effective on July 31, 2017 and expires on July 31, 2020. Further, in July 2017, we entered into an at-the-market 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 $50.0 million through Cowen pursuant to such universal shelf registration statement.

In April 2019, we raised $70.0 million in gross proceeds from the issuance of equity securities in two concurrent public offerings pursuant to the shelf registration statement, before deducting underwriting discounts and commissions and offering expenses of approximately $5.0 million.

During the year ended December 31, 2019, we raised aggregate gross proceeds of approximately $0.9 million pursuant to our at-the-market sales agreement with Cowen.

As of December 31, 2019, approximately $31.9 million of our common stock remained available for issuance under the at-the-market sales agreement.

As of December 31, 2019, $90.9 million of securities remained available for issuance under the shelf registration statement.

As of December 31, 2019, we had cash, cash equivalents and marketable securities of approximately $91.4 million.

In January 2020, we collected the $20.0 million upfront payment from our GBT collaboration and in February 2020 we drew down $20.0 million under our term loan with Oxford (See Note 14 to the consolidated financial statements included in Part II, Item 8 of this Annual Report on Form 10-K).

Cash Flows

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

	Year Ended December 31,		
	2019	2018	2017
Net cash (used in) provided by:			
Operating activities	$ (60,253)	$ (40,315)	$ (44,729)
Investing activities	(11,734)	(10,643)	(15,591)
Financing activities	65,990	69,084	33,937
Net (decrease) increase in cash, cash equivalents and restricted cash	$ (5,997)	$ 18,126	$ (26,383)

Net Cash Used in Operating Activities

The use of cash in all periods presented resulted primarily from our net losses adjusted for non-cash charges and changes in components of working capital.

Net cash used in operating activities was $60.3 million during the year ended December 31, 2019, compared to $40.3 million during the year ended December 31, 2018. The increase in cash used in operating activities was primarily due to a $13.1 million increase in our net loss from continuing operations and proceeds received upon entry into the Incyte target discovery collaboration during the year ended December 31, 2018 that did not recur in 2019.

Net cash used in operating activities was $40.3 million during the year ended December 31, 2018, compared to $44.7 million during the year ended December 31, 2017. The decrease in cash used in operating activities was primarily due to proceeds received upon entry into the Incyte target discovery collaboration during the year ended December 31, 2018.

Net Cash Used in Investing Activities

Net cash used in investing activities was $11.7 million during the year ended December 31, 2019, compared to $10.6 million during the year ended December 31, 2018. The increase in cash used in investing activities was primarily due to $12.6 million of purchases of property and equipment during the year ended December 31, 2019 as compared to $1.4 million for the year ended December 31, 2018 due to the buildout of our new corporate headquarters during the year ending December 31, 2019. This amount was offset by net maturities of marketable securities of $0.8 million for the year ended December 31, 2019, as compared to net purchases of $9.3 million for the year ended December 31, 2018.

Net cash used in investing activities was $10.6 million during the year ended December 31, 2018, compared to $15.6 million during the year ended December 31, 2017. The decrease in cash used in investing activities was primarily due to net purchases of marketable securities of $9.3 million during the year ended December 31, 2018, compared to net purchases of marketable securities of $14.8 million during the year ended December 31, 2017, as well as purchases of property and equipment of $1.4 million during the year ended December 31, 2018, as compared to purchases of property and equipment of $0.8 million during the year ended December 31, 2017.

Net Cash Provided by Financing Activities

Net cash provided by financing activities was $66.0 million during the year ended December 31, 2019, compared to net cash provided by financing activities of $69.1 million during the year ended December 31, 2018. Cash provided by financing activities for the year ended December 31, 2019 was primarily due to $65.0 million in net proceeds raised through two concurrent public offerings of equity securities that closed in April 2019, $0.8 million in net proceeds through the use of our at-the-market sales agreement, $0.2 million in proceeds through the sale of common stock through our employee stock purchase plan, and $0.2 million in proceeds through the exercise of stock options, offset by payments of $0.2 million under our capital lease obligations. Cash provided by financing activities for the year ended December 31, 2018 was primarily due to net proceeds of $42.8 million from the sale of our common stock in an underwritten public offering in February 2018, $1.4 million in proceeds from our February 2018 private placement, $7.7 million in proceeds attributable to the equity investment made by Incyte in connection with entry into our target discovery collaboration, $16.6 million in net proceeds through the use of our at-the-market sales facility, and $0.6 million from the exercise of employee stock options, offset by net payments under our capital lease obligations.

Net cash provided by financing activities was $69.1 million during the year ended December 31, 2018, compared to net cash provided by financing activities of $33.9 million during the year ended December 31, 2017. Cash provided by financing activities for the year ended December 31, 2018 was primarily due to net proceeds of $42.8 million from the sale of our common stock in an underwritten public offering in February 2018, $1.4 million in proceeds from our February 2018 private placement, $7.7 million in proceeds attributable to the equity investment made by Incyte in connection with entry into our target discovery collaboration, $16.6 million in net proceeds through the use of our at-the-market sales facility, and $0.6 million from the exercise of employee stock options, offset by payments under our capital lease obligations. Net cash provided by financing activities for the year ended December 31, 2017 was primarily attributable to the private placement of our common stock for gross proceeds of $35.0 million in April 2017, resulting in net proceeds of $32.6 million, and $1.8 million from the exercise of employee stock options

Funding Requirements

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue clinical trials of SY-1425, advance additional product candidates such as SY-5609 through preclinical development and into clinical trials, seek to develop companion diagnostic tests for use with our product candidates, initiate new research and preclinical development projects and seek marketing approval for any product candidates that we successfully develop. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to establishing sales, marketing, distribution and other commercial infrastructure to commercialize such products. We will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on favorable terms, we would be forced to delay, reduce, eliminate, or out-license our research and development programs or future commercialization rights to our product candidates.

We believe that our cash, cash equivalents and marketable securities as of December 31, 2019, together with the $20.0 million up-front license fee received from GBT in January 2020 in connection with entry into our sickle cell disease collaboration in December 2019 and the $20.0 million drawn down under our term loan from Oxford in February 2020, will enable us to fund our planned operating expense and capital expenditure requirements into 2022. Our future funding requirements, both short-term and long-term, will depend on many factors, including:

- the scope, progress, timing, costs and results of clinical trials of SY-1425 and SY-5609 and any associated companion diagnostic tests;
- the timing of wind-down activities for SY-1365 following our announcement in October 2019 that we are ceasing further development of that product candidate as part of a prioritization of our CDK7 product portfolio;
- research and preclinical development efforts for any future product candidates that we may develop;
- the number of future product candidates that we pursue and their development requirements;
- our ability to enter into, and the terms and timing of, any collaborations, licensing agreements or other arrangements;

- whether a drug candidate will be nominated to enter investigational new drug application-enabling studies under our sickle cell disease collaboration with GBT, whether GBT will exercise its option to exclusively license intellectual property arising from the collaboration, whether and when any option exercise fees, milestone payments or royalties under the collaboration agreement with GBT will ever be paid, and whether we exercise our U.S. co-promotion option under the GBT agreement;

- whether our target discovery collaboration with Incyte will yield any validated targets, whether Incyte will exercise any of its options to exclusively license intellectual property directed to such targets, and whether and when any of the target validation fees, option exercise fees, milestone payments or royalties under the collaboration agreement with Incyte will ever be paid;

- the outcome, timing and costs of seeking regulatory approvals;

- the costs of commercialization activities for any of our product candidates that receive marketing approval to the extent such costs are not the responsibility of any future collaborators, including the costs and timing of establishing product sales, marketing, distribution and manufacturing capabilities;

- the costs of acquiring potential new product candidates or technology;

- the costs of any physician education programs relating to selecting and treating genomically defined patient populations;

- the timing and amount of milestone and other payments due to licensors for patent and technology rights used in our gene control platform or to TMRC Co. Ltd., or TMRC, associated with the development, manufacture and commercialization of SY-1425;

- revenue received from commercial sales, if any, of our current and future product candidates;

- our headcount growth and associated costs as we advance our research and development programs and establish a commercial infrastructure; and

- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights and defending against intellectual property related claims.

Identifying potential product candidates and conducting preclinical studies and clinical trials is a time-consuming, expensive and uncertain process that takes many years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements. To the extent that we raise additional capital 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 involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

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

Off-Balance Sheet Arrangements

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

JOBS Act

In April 2012, the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, was enacted. Section 107 of the JOBS Act provides that an emerging growth company, or EGC, can take advantage of the extended transition period provided in Section 7(a)(2)(B) of the Securities Act of 1933, as amended, or the Securities Act, for complying with new or revised accounting standards. Thus, an EGC can delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this extended transition period and, as a result, we will adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required for other public companies.

As an EGC, we intend to rely on the exemption from the requirement to provide an auditor's attestation report on our system of internal controls over financial reporting pursuant to Section 404(b) of the Sarbanes-Oxley Act and with the exemption from any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements, known as the auditor discussion and analysis. We will remain an EGC until the earlier of (i) the last day of the fiscal year in which we have total annual gross revenues of $1.07 billion or more; (ii) the last day of the fiscal year following the fifth anniversary of the date of the closing of our IPO; (iii) the date on which we have issued more than $1.0 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under SEC rules.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to market risk related to changes in interest rates. 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, including cash equivalents, are in the form of money market funds and marketable securities and are invested in U.S. treasury or government obligations. However, because of the short-term nature of the duration of our portfolio and the low-risk profile of our investments, we believe an immediate 10% change in market interest rates would not be expected to have a material impact on the fair market value of our investments portfolio or on our financial condition or results of operations.

We are also exposed to market risk related to changes in foreign currency exchange rates. We contract with vendors that are located in Asia and Europe and certain invoices are denominated in foreign currencies. We are subject to fluctuations in foreign currency rates in connection with these arrangements. We do not currently hedge our foreign currency exchange rate risk. As of December 31, 2019, we had no significant liabilities denominated in foreign currencies.

Inflation generally affects us by increasing our cost of labor and clinical trial costs. We do not believe that inflation had a material effect on our business, financial condition or results of operations during the year ended December 31, 2019.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

SYROS PHARMACEUTICALS, INC.
INDEX TO FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

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

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Syros Pharmaceuticals, Inc. (the Company) as of December 31, 2019 and 2018, the related consolidated statements of operations, comprehensive loss, convertible preferred stock and stockholders' equity and cash flows for each of the three years in the period ended December 31, 2019, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2019 and 2018, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2019, in conformity with US generally accepted accounting principles.

Adoption of ASC 842

As discussed in Note 2 to the consolidated financial statements, the Company changed its method of accounting for leases in 2019 due to the adoption of Accounting Standards Update ("ASU") No. 2016-02, Leases (Topic 842), and related amendments.

Adoption of ASC 606

As discussed in Note 2 to the consolidated financial statements, the Company changed its method of accounting for revenue in 2018 due to the adoption of Accounting Standards Update (ASU) No. 2014-09, Revenue from Contracts with Customers (Topic 606), and the related amendments.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements 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 audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the 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 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 financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2014.
Boston, Massachusetts
March 5, 2020

SYROS PHARMACEUTICALS, INC.
CONSOLIDATED BALANCE SHEETS
(in thousands, except share and per share data)

	December 31, 2019	December 31, 2018
Assets		
Current assets:		
Cash and cash equivalents	$ 41,441	$ 49,886
Marketable securities	49,975	49,793
Accounts receivable and contract assets	20,158	—
Prepaid expenses and other current assets	2,649	1,417
Restricted cash, current portion	290	638
Total current assets	114,513	101,734
Property and equipment, net	15,210	3,861
Other long-term assets	490	881
Restricted cash, net of current portion	3,086	290
Right-of-use asset – operating lease	15,821	—
Right-of-use assets – financing leases	858	—
Total assets	$ 149,978	$ 106,766
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 5,853	$ 3,309
Accrued expenses	10,646	13,893
Deferred revenue, current portion	5,739	1,926
Deferred rent, current portion	—	392
Financing and capital lease obligations, current portion	241	9
Operating lease obligation, current portion	1,037	—
Total current liabilities	23,516	19,529
Deferred rent, net of current portion	—	353
Deferred revenue, net of current portion	22,639	8,276
Financing and capital lease obligations, net of current portion	621	22
Operating lease obligation, net of current portion	24,018	—
Commitments and contingencies (See Note 9)		
Stockholders' equity:		
Preferred stock, $0.001 par value; 10,000,000 shares authorized at December 31, 2019 and December 31, 2018; 0 shares issued and outstanding at December 31, 2019 and December 31, 2018, respectively	—	—
Common stock, $0.001 par value; 200,000,000 shares authorized at December 31, 2019 and December 31, 2018; 43,367,801 and 33,765,864 shares issued and outstanding at December 31, 2019 and December 31, 2018, respectively	43	34
Additional paid-in capital	372,100	296,100
Accumulated other comprehensive gain (loss)	24	(3)
Accumulated deficit	(292,983)	(217,545)
Total stockholders' equity	79,184	78,586
Total liabilities and stockholders' equity	$ 149,978	$ 106,766

See accompanying notes to consolidated financial statements.

SYROS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF OPERATIONS
(in thousands, except share and per share data)

	Year Ended December 31,		
	2019	2018	2017
Revenue	$ 1,982	$ 2,050	$ 1,101
Operating expenses:			
Research and development	58,245	50,182	41,896
General and administrative	21,478	16,164	13,891
Total operating expenses	79,723	66,346	55,787
Loss from operations	(77,741)	(64,296)	(54,686)
Other income, net	2,303	2,017	676
Net loss applicable to common stockholders	$ (75,438)	$ (62,279)	$ (54,010)
Net loss per share applicable to common stockholders - basic and diluted	$ (1.88)	$ (1.91)	$ (2.13)
Weighted-average number of common shares used in net loss per share applicable to common stockholders - basic and diluted	40,222,182	32,656,237	25,406,845

See accompanying notes to consolidated financial statements.

SYROS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS
(in thousands)

	Year Ended December 31,		
	2019	**2018**	**2017**
Net loss	$ (75,438)	$ (62,279)	$ (54,010)
Other comprehensive gain (loss):			
Unrealized holding gains (losses) on marketable securities	27	39	(33)
Comprehensive loss	$ (75,411)	$ (62,240)	$ (54,043)

See accompanying notes to consolidated financial statements.

SYROS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY
(in thousands except share data)

	Common Stock		Series A Convertible Preferred Stock					
	Number of Shares	Par Value	Number of Shares	Par Value	Additional Paid-In Capital	Accumulated Other Comprehensive (Loss) Gain	Accumulated Deficit	Stockholders' Equity
Balance at December 31, 2016	23,380,888	$ 23	—	$ —	$ 181,844	$ (9)	$ (101,256)	$ 80,602
Exercise of stock options and vesting of restricted stock awards	449,896	—	—	—	1,799	—	—	1,799
Issuance of common stock through private placement, net of issuance costs of $2,400	2,592,591	3	—	—	32,544	—	—	32,547
Stock-based compensation expense	—	—	—	—	4,419	—	—	4,419
Other comprehensive loss	—	—	—	—	—	(33)	—	(33)
Net loss	—	—	—	—	—	—	(54,010)	(54,010)
Balance at December 31, 2017	26,423,375	$ 26	—	$ —	220,606	$ (42)	$ (155,266)	$ 65,324
Exercise of stock options	214,533	—	—	—	626	—	—	626
Issuance of common stock to Incyte Corporation, net of issuance costs of $100	793,021	1	—	—	7,647	—	—	7,648
Issuance of common stock in underwritten public offering, net of issuance costs of $3,300	4,816,753	6	—	—	42,694	—	—	42,700
Issuance of common stock through private placement	144,505	—	—	—	1,380	—	—	1,380
Issuance of common stock at-the-market, net of issuance costs of $107	1,373,677	1	—	—	16,537	—	—	16,538
Stock-based compensation expense	—	—	—	—	6,610	—	—	6,610
Other comprehensive gain	—	—	—	—	—	39	—	39
Net loss	—	—	—	—	—	—	(62,279)	(62,279)
Balance at December 31, 2018	33,765,864	$ 34	—	$ —	$ 296,100	$ (3)	$ (217,545)	$ 78,586
Exercise of stock options	60,181	—	—	—	211	—	—	211
Issuance of common stock and accompanying warrants in underwritten public offering, net of issuance costs of $4,600	8,667,333	9	—	—	60,350	—	—	60,359
Issuance of preferred stock and accompanying warrants in underwritten public offering, net of issuance costs of $400	—	—	666	—	4,638	—	—	4,638
Conversion of preferred stock (1,000 to 1 conversion ratio)	666,000		(666)	—	—	—	—	—
Issuance of common stock at-the-market, net of issuance costs of $100	180,787	—	—	—	799	—	—	799
Issuance of shares under Employee Stock Purchase Plan	27,386				161	—	—	161
Exercise of warrants	250	—	—	—	2	—	—	2
Stock-based compensation expense	—	—	—	—	9,839	—	—	9,839
Other comprehensive gain	—	—	—	—	—	27	—	27
Net loss	—	—	—	—	—	—	(75,438)	(75,438)
Balance at December 31, 2019	43,367,801	$ 43	—	$ —	$ 372,100	$ 24	$ (292,983)	$ 79,184

See accompanying notes to consolidated financial statements

SYROS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)

	Year Ended December 31,		
	2019	2018	2017 (As Adjusted)
Operating activities			
Net loss	$ (75,438)	$ (62,279)	$ (54,010)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	2,521	1,604	1,527
Amortization of financing right-of-use asset	201	—	—
Gain on disposal of fixed assets and modification of lease	(181)	—	—
Stock-based compensation expense	9,839	6,610	4,419
Net amortization of premiums and discounts on marketable securities	(949)	(642)	(102)
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(783)	(500)	131
Accounts receivable	(20,158)	—	867
Other long-term assets	—	(34)	(365)
Accounts payable	1,493	888	141
Accrued expenses	(3,576)	4,191	3,533
Deferred revenue	18,176	10,202	(550)
Proceeds for tenant improvement incentive from landlord	7,237	—	—
Operating lease asset and liabilities	1,365	—	—
Deferred rent and lease incentive	—	(355)	(320)
Net cash used in operating activities	(60,253)	(40,315)	(44,729)
Investing activities			
Purchases of property and equipment	(12,638)	(1,384)	(821)
Proceeds from the disposition of property and equipment	110	9	—
Purchases of marketable securities	(108,206)	(96,768)	(41,770)
Maturities of marketable securities	109,000	87,500	27,000
Net cash used in investing activities	(11,734)	(10,643)	(15,591)
Financing activities			
Payments on financing and capital lease obligations	(205)	(50)	(168)
Proceeds from issuance of common stock through employee benefit plans	211	626	1,799
Proceeds from issuance of common stock through exercise of warrants	2	—	—
Proceeds from the issuance of common stock through employee stock purchase plan	161	—	—
Proceeds from issuance of common stock through at-the-market sales agreement, net of issuance costs	824	16,538	—
Proceeds from issuance of common stock and accompanying warrants in public offerings and private placements, net of issuance costs	60,359	51,970	32,306
Proceeds from issuance of convertible preferred stock and accompanying warrants in public offering, net of issuance costs	4,638	—	—
Net cash provided by financing activities	65,990	69,084	33,937
(Decrease) increase in cash, cash equivalents and restricted cash	(5,997)	18,126	(26,383)
Cash, cash equivalents and restricted cash (See Note 6)			
Beginning of period	50,814	32,688	59,071
End of period	$ 44,817	$ 50,814	$ 32,688
Supplemental disclosure of cash flow information:			
Cash paid for interest	$ 72	$ 2	$ 9
Cash paid for tax	$ 29	$ 7	$ —
Non-cash investing and financing activities:			
Property and equipment received but unpaid as of period end	$ 1,565	$ 268	$ 143
Asset acquired under operating lease	$ 16,240	$ —	$ —
Assets acquired under financing lease	$ 1,059	$ 28	$ —
Deferred financing costs incurred but unpaid as of period end	$ 58	$ —	$ —
Offering costs incurred but unpaid as of period end	$ 23	$ —	$ 13

See accompanying notes to consolidated financial statements.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements

1. Nature of Business

Syros Pharmaceuticals, Inc. (the "Company"), a Delaware corporation formed in November 2011, is a biopharmaceutical company seeking to redefine the power of small molecules to control the expression of genes.

The Company is subject to a number of risks similar to those of other early stage companies, including dependence on key individuals; risks inherent in the development and commercialization of medicines to treat human disease; competition from other companies, many of which are larger and better capitalized; risks relating to obtaining and maintaining necessary intellectual property protection; and the need to obtain adequate additional financing to fund the development of its product candidates and discovery activities. If the Company is unable to raise capital when needed or on favorable terms, it would be forced to delay, reduce, eliminate or out-license certain of its research and development programs or future commercialization rights to its product candidates.

In April 2019, the Company completed two concurrent underwritten public offerings of the Company's equity securities, which together resulted in gross proceeds to the Company of $70.0 million, before underwriting discounts and commissions and offering expenses of approximately $5.0 million. In one of the public offerings, the Company sold 8,667,333 shares of its common stock and accompanying Class A warrants (the "Warrants") to purchase 1,951,844 shares of the Company's common stock, at a combined price to the public of $7.50 per common share and accompanying Warrant. In the other public offering, the Company sold 666 shares of its Series A convertible preferred stock (the "Series A Stock"), and accompanying Warrants to purchase 166,500 shares of the Company's common stock, at a combined public offering price of $7,500 per share and accompanying Warrant. Each Warrant is immediately exercisable at an exercise price of $8.625 per share, subject to adjustment in certain circumstances, and will expire on October 10, 2022. During November 2019, the Company issued and sold an aggregate of 180,787 shares of its common stock to the public pursuant to its at-the-market sales facility, resulting in aggregate gross proceeds of $0.9 million.

The Company has incurred significant annual net operating losses in every year since its inception. It expects to continue to incur significant and increasing net operating losses for at least the next several years. The Company's net losses were $75.4 million, $62.3 million and $54.0 million for the years ended December 31, 2019, 2018 and 2017, respectively. As of December 31, 2019, the Company had an accumulated deficit of $293.0 million. The Company has not generated any revenues from product sales, has not completed the development of any product candidate and may never have a product candidate approved for commercialization. The Company has financed its operations to date primarily through the sale of equity securities and through license and collaboration agreements. The Company has devoted substantially all of its financial resources and efforts to research and development and general and administrative expense to support such research and development. The Company's net losses may fluctuate significantly from quarter to quarter and year to year. Net losses and negative cash flows have had, and will continue to have, an adverse effect on the Company's stockholders' equity and working capital. The Company believes that its cash, cash equivalents and marketable securities of $91.4 million as of December 31, 2019 will be sufficient to allow the Company to fund its current operating plan for a period of at least 12 months past the issuance date of these consolidated financial statements.

2. Summary of Significant Accounting Policies

Basis of Presentation

The Company's consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States ("U.S. GAAP"). Any reference in these notes to applicable guidance is meant to refer to the authoritative U.S. GAAP as found in the Accounting Standards Codification ("ASC") and Accounting Standards Updates ("ASU") of the Financial Accounting Standards Board ("FASB").

Principles of Consolidation

The accompanying consolidated financial statements include the accounts of Syros Pharmaceuticals, Inc. and its wholly owned subsidiaries, Syros Securities Corporation, a Massachusetts corporation formed by the Company in December 2014 to exclusively engage in buying, selling and holding securities on its own behalf, and Syros Pharmaceuticals (Ireland) Limited, an Irish limited liability company formed by the Company in January 2019. All intercompany transactions and balances have been eliminated in consolidation.

Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts in the financial statements and accompanying notes. Management considers many factors in selecting appropriate financial accounting policies and in developing the estimates and assumptions that are used in the preparation of the financial statements. Management must apply significant judgment in this process. In addition, other factors may affect estimates, which include, but are not limited to, expected business and operational changes, sensitivity and volatility associated with the assumptions used in developing estimates and whether historical trends are expected to be representative of future trends. Management's estimation process often may yield a range of potentially reasonable estimates and management must select an amount that falls within that range of reasonable estimates. On an ongoing basis, the Company's management evaluates its estimates, which include, but are not limited to, estimates related to revenue recognition, stock-based compensation expense, accrued expenses and income taxes. Actual results may differ from those estimates or assumptions.

Segment Information

Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision maker, or decision-making group, in making decisions on how to allocate resources and assess performance. The Company's chief operating decision maker is the Chief Executive Officer. The Company and the chief operating decision maker view the Company's operations and manage its business in one operating segment. The Company operates only in the United States.

Cash and Cash Equivalents

The Company considers all highly liquid instruments that have original maturities of three months or less when acquired to be cash equivalents. Cash equivalents, which consist of money market funds that invest in U.S. Treasury obligations, as well as overnight repurchase agreements, are stated at fair value. The Company maintains its bank accounts at one major financial institution.

Off-Balance Sheet Risk and Concentrations of Credit Risk

The Company has no financial instruments with off-balance sheet risk, such as foreign exchange contracts, option contracts, or other foreign hedging arrangements. Financial instruments that potentially subject the Company to concentrations of credit risk primarily consist of cash equivalents and marketable securities. Under its investment policy, the Company limits amounts invested in such securities by credit rating, maturity, industry group, investment type and issuer, except for securities issued by the U.S. government. The Company is not exposed to any significant concentrations of credit risk from these financial instruments. The goals of the Company's investment policy, in order of priority, are safety and preservation of principal and liquidity of investments sufficient to meet cash flow requirements.

Fair Value of Financial Instruments

ASC 820, *Fair Value Measurement* ("ASC 820"), established a fair value hierarchy for instruments measured at fair value that distinguishes between assumptions based on market data (observable inputs) and the Company's own assumptions (unobservable inputs). Observable inputs are inputs that market participants would use in pricing the asset or liability based on market data obtained from sources independent of the Company. Unobservable inputs are inputs that reflect the Company's assumption about the inputs that market participants would use in pricing the asset or liability. These are developed based on the best information available under the circumstances.

ASC 820 identified fair value as the exchange price, or exit price, representing the amount that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. As a basis for considering market participant assumptions in fair value measurements, ASC 820 established a three-tier fair value hierarchy that distinguishes between the following:

Level 1—Quoted market prices (unadjusted) in active markets for identical assets or liabilities.

Level 2—Inputs other than quoted prices included within Level 1 that are either directly or indirectly observable, such as quoted market prices, interest rates and yield curves.

Level 3—Unobservable inputs developed using estimates or assumptions developed by the Company, which reflect those that a market participant would use.

To the extent that the valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized as Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

The carrying amounts reflected in the consolidated balance sheets for cash and cash equivalents, prepaid expenses, other current assets, restricted cash, accounts payable, accrued expenses, deferred revenue, and financing and operating lease liabilities approximate their respective fair values due to their short-term nature.

Property and Equipment

Property and equipment consists of laboratory equipment, computer equipment, furniture and fixtures and leasehold improvements, all of which are stated at cost, less accumulated depreciation. Expenditures for maintenance and repairs that do not improve or extend the lives of the respective assets are recorded to expense as incurred. Major betterments are capitalized as additions to property and equipment. Depreciation and amortization is recognized over the estimated useful lives of the assets using the straight-line method.

Construction-in-progress is stated at cost, which relates to the cost of leasehold improvements not yet placed into service. No depreciation expense is recorded on construction-in-progress until such time as the relevant assets are completed and put into use.

Impairment of Long-Lived Assets

The Company continually evaluates long-lived assets for potential impairment when events or changes in circumstances indicate the carrying value of the assets may not be recoverable. Recoverability is measured by comparing the book values of the assets to the expected future net undiscounted cash flows that the assets are expected to generate. If such assets are considered to be impaired, the impairment to be recognized is measured by the amount by which the book values of the assets exceed their fair value. The Company has not recognized any impairment losses from inception through December 31, 2019.

Other Long-Term Assets

At December 31, 2019, other long-term assets primarily consisted of advance payments made to the contract research organization responsible for conducting the Company's SY-1425 clinical trial. At December 31, 2018, other long-term assets primarily consisted of advance payments made to the contract research organization responsible for conducting the Company's clinical trials of SY-1425 and SY-1365.

Revenue Recognition

To date the Company's only revenue has consisted of collaboration and license revenue. The Company has not generated any revenue from product sales and does not expect to generate any revenue from product sales for the foreseeable future. For the years ended December 31, 2019 and 2018, the Company recognized approximately $2.0 million and $2.1 million of revenue, respectively, all of which is attributable to the Company's target discovery collaboration with Incyte Corporation ("Incyte"). For the year ended December 31, 2017, the Company recognized $1.1 million of revenue, all of which was attributable to a research agreement with a multinational pharmaceutical company that expired in accordance with its terms in March 2017.

The Company recognizes revenue in accordance with ASC 606, *Revenue from Contracts with Customers* ("ASC 606"). ASC 606 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. Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs 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) the entity satisfies a performance obligation.

The Company only applies the five-step model to contracts when it is probable that the entity will collect the consideration it is entitled to in exchange for the goods or services it transfers to the customer. If a contract is determined to be within the scope of ASC 606 at inception, the Company assesses the goods or services promised within such contract, determines which of those goods and services are performance obligations, and assesses whether each promised good or service is distinct. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

If the Company performs by transferring goods or services to a customer before the customer pays consideration or before payment is due, the Company records a contract asset, excluding any amounts presented as accounts receivable. The Company includes contract assets as unbilled accounts receivable on its consolidated balance sheets. The Company records accounts receivable for amounts billed to the customer for which the Company has an unconditional right to consideration. The Company assesses contract assets and accounts receivable for impairment and, to date, no impairment losses have been recorded.

From time to time, the Company may enter into agreements that are within the scope of ASC 606. The terms of these arrangements typically include payment to the Company of one or more of the following: non-refundable, up-front license fees or prepaid research and development services; development, regulatory and commercial milestone payments; and royalties on net sales of licensed products. Each of these payments results in license and collaboration revenues, except for revenues from royalties on net sales of licensed products, which will be classified as royalty revenues.

The Company analyzes its collaboration arrangements to assess whether they are within the scope of ASC 808, *Collaborative Arrangements* ("ASC 808"), to determine whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities. This assessment is performed throughout the life of the arrangement based on changes in the responsibilities of all parties in the arrangement. For collaboration arrangements within the scope of ASC 808 that contain multiple elements, the Company first determines which elements of the collaboration are deemed to be within the scope of ASC 808 and those that are more reflective of a vendor-customer relationship and therefore within the scope of ASC 606. For elements of collaboration arrangements that are accounted for pursuant to ASC 808, an appropriate recognition method is determined and applied consistently, generally by analogy to ASC 606. For those elements of the arrangement that are accounted for pursuant to ASC 606, the Company applies the five-step model described above.

Prior to January 1, 2018, the Company analyzed arrangements with multiple deliverables based on the guidance in ASC Topic 605-25, *Revenue Recognition—Multiple Element Arrangements* ("ASC 605-25"). Pursuant to the guidance in ASC 605-25, the Company evaluated multiple element arrangements to determine (1) the deliverables included in the arrangement and (2) whether the individual deliverables represent separate units of accounting or whether they must be accounted for as a combined unit of accounting. This evaluation involved subjective determinations and required management to make judgements about the individual deliverables and whether such deliverables were separate from other aspects of the contractual relationship. Deliverables were considered separate units of accounting provided that: (i) the delivered item(s) had value to the customer on a standalone basis and (ii) if the arrangement included a general right of return relative to the delivered item(s), delivery or performance of the undelivered item(s) was considered probable and substantially within control of the Company.

The Company recognized arrangement consideration allocated to each unit of accounting when all of the revenue recognition criteria in ASC 605 were satisfied for that particular unit of accounting. In the event that a deliverable did not represent a separate unit of accounting, the Company recognized revenue from the combined unit of accounting over the contractual or estimated performance period for the undelivered items, which was typically the term of its research and development obligations. If there was no discernible pattern of performance or objectively measurable performance measures did not exist, then the Company recognized revenue under the arrangement on a straight-line basis over the period it expected to complete its performance obligations, or upon completion when the final act was of such significance to the overall arrangement that performance would not have substantively occurred until the completion of that act. Conversely, if the pattern of performance over which the service was provided to the customer could not be determined and objectively measurable performance measures existed, then the Company recognized revenue under the arrangement using the proportional performance method.

Research and Development

Expenditures relating to research and development are expensed in the period incurred. Research and development expenses consist of both internal and external costs associated with the development of our gene control platform and product candidates. Research and development costs include salaries and benefits, materials and supplies, external research, preclinical and clinical development expenses, stock-based compensation expense and facilities costs. Facilities costs primarily include the allocation of rent, utilities, depreciation and amortization.

In certain circumstances, the Company is required to make nonrefundable advance payments to vendors for goods or services that will be received in the future for use in research and development activities. In such circumstances, the nonrefundable advance payments are deferred and capitalized, even when there is no alternative future use for the research and development, until related goods or services are provided.

The Company records accruals for estimated ongoing research costs. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the work being performed, including the phase or completion of the event, invoices received and costs. Significant judgements and estimates may be made in determining the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates.

The Company may in-license the rights to develop and commercialize product candidates. For each in-license transaction the Company evaluates whether it has acquired processes or activities along with inputs that would be sufficient to constitute a "business" as defined under U.S. GAAP. A "business" as defined under U.S. GAAP consists of inputs and processes applied to those inputs that have the ability to create outputs. Although businesses usually have outputs, outputs are not required for an integrated set of activities to qualify as a business. When the Company determines that it has not acquired sufficient processes or activities to constitute a business, any up-front payments, as well as milestone payments, are immediately expensed as acquired research and development in the period in which they are incurred.

Stock-Based Compensation Expense

The Company accounts for its stock-based compensation awards in accordance with ASC 718, *Compensation—Stock Compensation* ("ASC 718"). ASC 718 requires all stock-based payments to employees and directors, including grants of restricted stock units and stock option awards, to be recognized as expense in the consolidated statements of operations based on their grant date fair values. Effective January 1, 2019, grants of restricted stock units and stock option awards to other service providers, referred to as non-employees, are measured based on the grant-date fair value of the award and expensed in the Company's consolidated statement of operations over the vesting period. Through December 31, 2018, grants of restricted stock unit and stock option awards to non-employees were required to be recognized as expense in the consolidated statements of operations based on their vesting date fair values. The Company estimates the fair value of stock options granted using the Black-Scholes option-pricing model. Prior to June 30, 2016, the Company was a private company and, therefore, lacks Company-specific historical and implied volatility information. As a result, the Company estimates its expected stock volatility based on the historical volatility of a publicly traded set of peer companies and expects to continue to do so until such time as it has adequate historical data regarding the volatility of its own traded stock price. The expected term of the Company's stock options has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" options. Through December 31, 2018, the expected term of stock options granted to non-employees was equal to the contractual term of the option award. Effective January 1, 2019, the expected term of stock options to non-employees can be determined using either the contractual term of the option award or the "simplified" method. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. Expected dividend yield is based on the fact that the Company has never paid cash dividends and does not expect to pay any cash dividends in the foreseeable future. The Company uses the value of its common stock to determine the fair value of restricted stock awards.

The Company expenses the fair value of its stock-based awards to employees and non-employees on a straight-line basis over the associated service period, which is generally the vesting period. The Company accounts for forfeitures as they occur instead of estimating forfeitures at the time of grant. Ultimately, the actual expense recognized over the vesting period will be for only those options that vest.

Compensation expense for discounted purchases under the employee stock purchase plan is measured using the Black-Scholes model to compute the fair value of the lookback provision plus the purchase discount and is recognized as compensation expense over the offering period.

For stock-based awards that contain performance-based milestones, we record stock-based compensation expense in accordance with the accelerated attribution model. Management evaluates when the achievement of a performance-based milestone is probable based on the expected satisfaction of the performance conditions as of the reporting date. For certain of our performance-based awards, notwithstanding any vesting in accordance with the achievement of performance-based milestones, such awards vest in full on the sixth anniversary of the vesting commencement date. Compensation expense for such awards is recognized over the six-year vesting period unless management determines that the achievement of any performance-based milestones is probable, in which case expense is accelerated.

Income Taxes

The Company accounts for uncertain tax positions using a more-likely-than-not threshold for recognizing and resolving uncertain tax positions. The evaluation of uncertain tax positions is based on factors including, but not limited to, changes in the law, the measurement of tax positions taken or expected to be taken in tax returns, the effective settlement of matters subject to audit, new audit activity, and changes in facts or circumstances related to a tax position.

Net Loss per Share

Basic net earnings per share applicable to common stockholders is calculated by dividing net earnings applicable to common stockholders by the weighted average shares outstanding during the period, without consideration for common stock equivalents. Diluted net earnings per share applicable to common stockholders 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 and the if-converted method. For purposes of the calculation of dilutive net loss per share applicable to common stockholders, stock options, unvested restricted stock units, and warrants are considered to be common stock equivalents but are excluded from the calculation of diluted net loss per share applicable to common stockholders, as their effect would be anti-dilutive; therefore, basic and diluted net loss per share applicable to common stockholders were the same for all periods presented.

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:

	As of December 31,		
	2019	2018	2017
Stock options	4,618,421	3,732,643	2,846,668
Unvested restricted stock units	1,116,358	—	—
Warrants	2,118,094	—	—
Total	7,852,873	3,732,643	2,846,668

The weighted average number of common shares used in net loss per share applicable to common stockholders on a basic and diluted basis were 40,222,182, 32,656,237 and 25,406,845 shares for the years ended December 31 2019, 2018 and 2017, respectively.

Recent Accounting Pronouncements

In April 2019, the FASB issued ASU No. 2019-04, *Codification Improvements to Topic 326 Financial Instruments – Credit Losses, Topic 815, Derivatives and Hedging, and Topic 825* ("ASU 2019-04"). ASU 2019-04 clarifies the accounting treatment for the measurement of credit losses under ASC 236 and provides further clarification on previously issued updates including ASU 2017-12, *Derivatives and Hedging (Topic 815): Targeted Improvements to Accounting for Hedging Activities* and ASU 2016-01, *Financial Instruments—Overall (Subtopic 825-10): Recognition and Measurement of Financial Assets and Financial Liabilities*. ASU 2019-04 is effective for fiscal years beginning after December 15, 2020, including interim periods within those fiscal years. Early adoption is permitted. The Company is currently in the process of evaluating the new standard but does not anticipate ASU 2019-14 will have a material impact on its consolidated financial statements and related disclosures.

In November 2018, the FASB issued ASU No. 2018-18, Collaborative Arrangements (Topic 808): Clarifying the Interaction between Topic 808 and Topic 606, Revenue from Contracts with Customers ("ASU 2018-18"). ASU 2018-18 (1) clarifies that certain transactions between collaborative arrangement participants should be accounted for under ASC 606, when the collaborative arrangement participant is a customer in the context of a unit of account, (2) adds unit-of-account guidance in ASC 808 to align with ASC 606 when an entity is assessing whether the collaborative arrangement, or a part of the arrangement, is within the scope of ASC 606, (3) precludes presenting transactions together with revenue when those transactions involve collaborative arrangement participants that are not directly related to third parties and are not customers. The standard will be effective for fiscal years beginning after December 15, 2019, and interim periods within those fiscal years, with early adoption permitted. The company is currently evaluating the impact of adoption of ASU 2018-18 on its consolidated financial statements and related disclosures.

In August 2018, the FASB issued ASU No. 2018-13, *Fair Value Measurements (Topic 820)* ("ASU 2018-13"), which provides for changes to the disclosure requirements for recurring and nonrecurring fair value measurements under Topic 820. ASU 2018-13 is effective for fiscal years and interim periods within those fiscal years beginning after December 15, 2019. Provisions of ASU 2018-13 including changes in unrealized gains and losses, the range and weighted average of significant unobservable inputs used to develop Level 3 fair value measurements, and the narrative description of measurement uncertainty are required to be applied prospectively for only the most recent interim or annual period presented in the initial fiscal year of adoption. All other amendments in ASU 2018-13 will be applied retrospectively to all periods presented upon their effective date. Early adoption is permitted upon issuance of ASU 2018-13. The Company is currently in the process of evaluating the new standard but does not anticipate ASU 2018-13 will have a material impact on its consolidated financial statements and related disclosures.

Recently Adopted Accounting Pronouncements

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842)* ("ASC 842"), which applies to all leases and requires lessees to record most leases on the balance sheet but recognize expense in a manner similar to the previous standard. ASC 842 is effective for fiscal years beginning after December 15, 2018 and interim periods within those years and, as such, is effective starting January 1, 2019 for the Company. Entities are required to use a modified retrospective approach of adoption for leases that exist or are entered into after the beginning of the earliest comparative period in the financial statements. Full retrospective application is prohibited. The modified retrospective approach includes a number of optional practical expedients primarily focused on leases that commenced before the effective date of ASC 842, including continuing to account for leases that commence before the effective date in accordance with previous guidance, unless the lease is modified. In July 2018, the FASB issued ASU No. 2018-11, *Leases*: *Targeted Improvements*, which clarifies ASC 842 and provides companies with an optional transition method. The optional transition method allows for companies to adopt ASC 842 as of the January 1, 2019 adoption date and record a cumulative catch-up to related earnings during the period of adoption. The Company adopted ASC 842 on January 1, 2019 and elected to use the practical expedients and therefore the Company is only presenting right-of-use assets and lease liabilities as of the adoption date and additionally elected to not reassess the classification of leases executed prior to the January 1, 2019 adoption date. The Company has also elected the practical expedient provided under ASC 842 for its operating and finance leases and will combine lease and non-lease components at the time of execution of the applicable lease. The primary effect of the new standard, as of the adoption date, was the recording of a right-of-use asset and lease liability for the operating lease for the Company's former office and laboratory facility at 620 Memorial Drive, Cambridge, Massachusetts. As of the January 1, 2019 adoption date, the Company recorded (i) a lease liability of $2.2 million, of which $1.1 million was classified as short-term and $1.1 million as long-term, which represented the present value of remaining lease payments as of the adoption date, discounted using an incremental borrowing rate of 10% and (ii) a right-of-use asset of approximately $1.5 million classified as long-term, which represented a corresponding amount to the lease liability of $2.2 million adjusted for deferred rent of approximately $0.7 million. The Company also had two immaterial capital leases that, as of the adoption date, were classified as financing leases, with the underlying assets recorded as part of property and equipment, net, in the Company's consolidated balance sheets.

In June 2018, the FASB issued ASU No. 2018-07, *Compensation -Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* ("ASU 2018-07"). ASU 2018-07 aims to simplify the accounting for share-based payments to nonemployees by aligning it to the accounting for share-based payments to employees including determining the fair value of the award on the date of grant and recognizing the stock-based compensation expense as of the respective vesting date. The new standard also requires companies to elect to either measure the awards to non-employees over an estimated expected term or contractual term as well as elect to estimate forfeitures or account for forfeitures as they occur. ASU 2018-07 is effective for fiscal years and interim periods within those fiscal years beginning after December 15, 2018 and is to be adopted using a modified retrospective approach with a cumulative catch-up to retained earnings recorded for equity-classified awards for which a measurement date has not been established as of the date of adoption. The Company adopted ASU 2018-07 effective January 1, 2019, and the adoption of the new standard did not have a material impact on the Company's consolidated financial statements and related disclosures.

3. Collaboration and Research Arrangements

Collaboration with Global Blood Therapeutics

On December 17, 2019, the Company entered into a license and collaboration agreement (the "GBT Collaboration Agreement") with Global Blood Therapeutics, Inc. ("GBT"), pursuant to which the parties agreed to a research collaboration to discover novel targets that induce fetal hemoglobin in order to develop new small molecule treatments for sickle cell disease and beta thalassemia. The research term (the "Research Term") is for an initial period of three years and can be extended for up to two (2) additional one-year terms upon mutual agreement.

Pursuant to the terms of the GBT Collaboration Agreement, GBT agreed to pay the Company an upfront payment of $20.0 million, which was collected in January 2020. GBT also agreed to reimburse the Company for full-time employee and out-of-pocket costs and expenses incurred by the Company in accordance with the agreed-upon research budget, which is anticipated to total approximately $40.0 million over the initial Research Term.

The Company granted to GBT an option (the "Option") to obtain an exclusive, worldwide license, with the right to sublicense, under relevant intellectual property rights and know-how of the Company arising from the collaboration to develop, manufacture and commercialize any compounds or products resulting from the collaboration. GBT may exercise the Option at any time during the period (i) commencing on the earlier of (a) the date of GBT's designation of the first product candidate to enter investigational new drug application-enabling studies, or (b) if no such candidate is designated as of the expiration of the Research Term, the date of expiration of the Research Term, and (ii) ending on the 180th day after the date of expiration or earlier termination of the Research Term. GBT's exercise of the Option will be subject to any required filings with the applicable antitrust authority as required by the antitrust laws and satisfaction of any applicable antitrust conditions.

Should GBT exercise its Option, the Company could receive up to $315.0 million in option exercise, development, regulatory, commercialization and sales-based milestones per product candidate and product resulting from the collaboration.

The Company will also be entitled to receive, subject to certain reductions, tiered mid-to-high single digit royalties as percentages of calendar year net sales on any product.

Either party may terminate the GBT Collaboration Agreement for the other party's uncured material breach or insolvency, and in certain other specified circumstances, subject to specified notice and cure periods. GBT may unilaterally terminate the GBT Collaboration Agreement in its entirety, for any or no reason, upon nine-months' prior written notice to the Company if such notice is delivered during the Research Term, or 90 days' prior written notice to the Company if such notice is delivered after the expiration or termination of the Research Term.

GBT Collaboration Revenue

The Company analyzed the GBT Collaboration Agreement and concluded that it represents a contract with a customer within the scope of ASC 606.

The Company has identified a single performance obligation, which includes a (i) non-exclusive research license that GBT will have access to during the initial Research Term and (ii) research and development services provided during the initial Research Term. The GBT Collaboration Agreement includes the Option. The Option does not provide a material right to GBT that it would receive without entering into the GBT Collaboration Agreement, principally because the Option exercise fee is at least equal to the standalone selling price for the underlying goods. The non-exclusive research license is not distinct as GBT cannot benefit from the license without the research and development services that are separately identifiable in the contract. The non-exclusive research license only allows GBT to evaluate the candidate compounds developed under the research plan or to conduct work allocated to it during the Research Term. GBT cannot extract any benefit from the non-exclusive research license without the research and development services performed by the Company, including the provision of data package information. As such, these two promises are inputs to a combined output (the delivery of data package allowing GBT to make an Option exercise decision) and are bundled into a single performance obligation (the non-exclusive research license and research and development service performance obligation).

At inception, the total transaction price was determined to be approximately $60.0 million, which consisted of a $20.0 million upfront non-refundable and non-creditable technology access fee and approximately $40.0 million in reimbursable costs for employee and external research and development expenses. The GBT Collaboration Agreement also provides for development and regulatory milestones which are only payable subsequent to the exercise of the Option, and therefore are excluded from transaction price at inception. The Company will re-evaluate the transaction price at the end of each reporting period and as uncertain events are resolved or other changes in circumstances occur.

ASC 606 requires an entity to recognize revenue only when it satisfies a performance obligation by transferring a promised good or service to a customer. A good or service is considered to be transferred when the customer obtains control. As the non-exclusive research license and research and development services represent one performance obligation, the Company has determined that it will satisfy its performance obligation over a period of time as services are performed and GBT receives the benefit of the services, as the overall purpose of the arrangement is for the Company to perform the services. The Company will recognize revenue associated with the performance obligation as the research and development services are provided using an input method, according to the costs incurred as related to the research and development activities and the costs expected to be incurred in the future to satisfy the performance obligation. The transfer of control occurs during this time and is the best measure of progress towards satisfying the performance obligation.

As of December 31, 2019, the Company recorded an accounts receivable balance of $20.0 million and $20.0 million of deferred revenue, of which $4.5 million and $15.5 million, was classified as deferred revenue, current portion and deferred revenue, net of current portion, respectively, on the Company's consolidated balance sheets. In January 2020, the $20.0 million payment was collected.

No revenue was recognized under the GBT Collaboration Agreement during the year ended December 31, 2019.

Agreements with Incyte Corporation

In January 2018, the Company and Incyte entered into a Target Discovery, Research Collaboration and Option Agreement (the "Incyte Collaboration Agreement"). The Incyte Collaboration Agreement was amended in November 2019. Under the Incyte Collaboration Agreement, the Company is using its proprietary gene control platform to identify novel therapeutic targets with a focus on myeloproliferative neoplasms, and Incyte has received options to obtain exclusive worldwide rights to intellectual property resulting from the collaboration for the development and commercialization of therapeutic products directed to up to seven validated targets. For each option exercised by Incyte, Incyte will have the exclusive worldwide right to use the licensed intellectual property to develop and commercialize therapeutic products that modulate the target as to which the option was exercised. Under the terms of the Collaboration Agreement, Incyte paid the Company $10.0 million in up-front consideration, consisting of $2.5 million in cash and $7.5 million in pre-paid research funding (the "Prepaid Research Amount"). The Company's activities under the Collaboration Agreement are subject to a joint research plan and, subject to certain exceptions, Incyte is responsible for funding the Company's activities under the research plan, including amounts in excess of the Prepaid Research Amount.

In January 2018, the Company also entered into a Stock Purchase Agreement with Incyte (the "Stock Purchase Agreement") whereby, for an aggregate purchase price of $10.0 million, Incyte purchased 793,021 shares of the Company's common stock at $12.61 per share. Under the terms of the Stock Purchase Agreement, the shares were purchased at a 30% premium over the volume-weighted sale price of the shares of the Company's common stock over the 15-trading day period immediately preceding the date of the Stock Purchase Agreement.

Incyte Collaboration Revenue

The Company analyzed the Incyte Collaboration Agreement and concluded that it represents a contract with a customer within the scope of ASC 606.

The Company identified a single performance obligation which includes (i) a research license that Incyte retains as long as there remains an unexercised option (the "Research License") and (ii) research and development services provided during the research term. The Incyte Collaboration Agreement includes options to (x) obtain additional time to exercise the license options for certain targets designated as definitive validation targets and (y) obtain license rights to each validated target, both of which were not considered by the Company's management to be material rights, and therefore not performance obligations, at inception.

At inception, the total transaction price was determined to be $12.3 million. Following a November 2019 amendment, the total transaction price is now $12.8 million, consisting of a $2.5 million upfront non-refundable and non-creditable payment, the $7.5 million Prepaid Research Amount and $2.3 million in premium paid on the equity investment made pursuant the Stock Purchase Agreement and $0.5 million of additional consideration. The Company accounted for the contract amendment as a modification as if it were part of the existing contract as the remaining goods and services are not distinct, and therefore form part of a single performance obligation that was partially satisfied at the date of the amendment. This additional consideration will be recognized on a percent complete basis as work is performed.

The Incyte Collaboration Agreement also provides for development and regulatory milestones that are only payable subsequent to the exercise of an option and were therefore excluded from transaction price at inception. The Company intends to re-evaluate the transaction price at the end of each reporting period and as uncertain events are resolved or other changes in circumstances occur.

The Incyte Collaboration Agreement also provides for development and regulatory milestones that are only payable subsequent to the exercise of an option and were therefore excluded from transaction price at inception. The Company intends to re-evaluate the transaction price at the end of each reporting period and as uncertain events are resolved or other changes in circumstances occur.

The Company recognizes revenue associated with the performance obligation as the research and development services are provided using an input method, according to the costs incurred as related to the research and development activities and the costs expected to be incurred in the future to satisfy the performance obligation. The transfer of control occurs during this time and is the best measure of progress towards satisfying the performance obligation.

During the years ended December 31, 2019 and 2018, the Company recognized $2.0 million and $2.1 million of revenue, respectively, under the Incyte Collaboration Agreement. As of December 31, 2019, the Company has deferred revenue outstanding under the Incyte Collaboration Agreement of approximately $8.4 million, of which $1.3 million and $7.1 million were classified as deferred revenue, current portion and deferred revenue, net of current portion, respectively, on the Company's consolidated balance sheets.

Other Research Agreements

In November 2014, the Company entered into a research agreement with a multinational pharmaceutical company for purposes of mapping immune cell super-enhancers and transcriptional targets in autoimmune disease. The Company recognized revenue on a completed performance basis for each project performed under the agreement, as the Company did not have the ability to reasonably estimate the period of performance and the final study report for each project was significant to the overall arrangement. The Company recognized revenue of $1.1 million during the year ended December 31, 2017 under the agreement. The research agreement terminated automatically on March 31, 2017 in accordance with its terms.

The following table presents the changes in contract assets and liabilities for the year ended December 31, 2019 (in thousands):

	Balance at December 31, 2018	Additions	Deductions	Balance at December 31, 2019
Contract assets:				
Billed and unbilled receivables from collaboration partners	$ —	$ 20,158	$ —	$ 20,158
Contract liabilities:				
Deferred revenue - Incyte	$ 10,202	$ 158	$ 1,982	$ 8,378
Deferred revenue - GBT	—	20,000	—	20,000
Total	$ 10,202	$ 20,158	$ 1,982	$ 28,378

The change in deferred revenue is due to the addition of $20.0 million of deferred revenue following the execution of the GBT Collaboration Agreement in December 2019 and the recording of the $20.0 million upfront payment due and the addition of $0.2 million of incurred but unbilled consideration out of the amendment to the Incyte Collaboration Agreement. These were offset by the recognition of $2.0 million of revenue under the Incyte Collaboration Agreement.

4. Cash, Cash Equivalents and Marketable Securities

Cash equivalents are highly liquid investments that are readily convertible into cash with original maturities of three months or less when purchased. Marketable securities consist of securities with original maturities greater than 90 days when purchased. The Company classifies these marketable securities as available-for-sale and records them at fair value in the accompanying consolidated balance sheets. Unrealized gains or losses are included in accumulated other comprehensive loss. Premiums or discounts from par value are amortized to other income over the life of the underlying security.

Cash equivalents and marketable securities, available-for-sale, consisted of the following at December 31, 2019 and December 31, 2018 (in thousands):

December 31, 2019	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
Cash and cash equivalents:				
Cash and money market funds	$ 29,441	$ —	$ —	$ 29,441
Overnight repurchase agreements	12,000	—	—	12,000
Marketable securities:				
U.S. treasury obligations	49,951	24	—	49,975
Total:	$ 91,392	$ 24	$ —	$ 91,416

December 31, 2018	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
Cash and cash equivalents:				
Cash and money market funds	$ 34,886	$ —	$ —	$ 34,886
Overnight repurchase agreements	15,000	—	—	15,000
Marketable securities:				
U.S. treasury obligations	49,796	—	(3)	49,793
Total:	$ 99,682	$ —	$ (3)	$ 99,679

Although available to be sold to meet operating needs or otherwise, securities are generally held through maturity. The cost of securities sold is determined based on the specific identification method for purposes of recording realized gains and losses. During, the years ended December 31, 2019, 2018 and 2017, there were no realized gains or losses on sales of investments, and no investments were adjusted for other than temporary declines in fair value.

As of December 31, 2019 and 2018, all marketable securities had maturities of less than twelve months when purchased.

At December 31, 2019, the Company did not hold any securities that were in an unrealized loss position.

5. Fair Value Measurements

Assets measured at fair value on a recurring basis as of December 31, 2019 and December 31, 2018 were as follows (in thousands):

Description	December 31, 2019	Active Markets (Level 1)	Observable Inputs (Level 2)	Unobservable Inputs (Level 3)
Cash and cash equivalents:				
Cash and money market funds	$ 29,441	$ 29,441	$ —	$ —
Overnight repurchase agreements	12,000	—	12,000	—
Marketable securities:				
U.S. treasury obligations	49,975	49,975	—	—
	$ 91,416	$ 79,416	$ 12,000	$ —

Description	December 31, 2018	Active Markets (Level 1)	Observable Inputs (Level 2)	Unobservable Inputs (Level 3)
Cash and cash equivalents:				
Cash and money market funds	$ 34,886	$ 34,886	$ —	$ —
Overnight repurchase agreements	15,000	—	15,000	—
Marketable securities:				
U.S. treasury obligations	49,793	49,793	—	—
	$ 99,679	$ 84,679	$ 15,000	$ —

6. Restricted Cash

At December 31, 2019, the Company had $3.4 million in restricted cash, of which $0.3 million was classified as short-term and $3.1 million as long-term on the Company's consolidated balance sheets.

The Company's letter of credit for the 2015 Lease (See Note 9) is classified as current on the Company's consolidated balance sheets as of December 31, 2019.

In connection with the execution of the 2019 Lease (See Note 9), the Company was required to provide the landlord with a letter of credit in the amount of $3.1 million that will expire 95 days after expiration or early termination of the 2019 Lease. The Company will have the right, under certain conditions, to reduce the amount of the letter of credit to $2.1 million in October 2023. The $3.1 million letter of credit was classified as long-term restricted cash on the Company's consolidated balance sheet as of December 31, 2019.

At December 31, 2018, the Company had $0.9 million in restricted cash, of which $0.6 million was classified as short-term and $0.3 million as long-term on the Company's consolidated balance sheets.

In August 2018, the Company entered into a manufacturing agreement with a third party for manufacturing services related to one of its product candidates. In accordance with the terms of the manufacturing agreement, the Company was required to provide a letter of credit in the amount of $0.6 million. In October 2019, the third-party manufacturer released the Company from the letter of credit in accordance with the terms of the manufacturing agreement. In connection with this release, the Company collected the $0.6 million in full and the letter of credit is no longer outstanding.

The following table provides a reconciliation of cash, cash equivalents, and restricted cash reported within the consolidated balance sheets that sum to the total of the amounts shown in the consolidated statement of cash flows as of December 31, 2019, 2018, 2017 and 2016 (in thousands):

	December 31, 2019	December 31, 2018	December 31, 2017	December 31, 2016
Cash and cash equivalents	$ 41,441	$ 49,886	$ 32,205	$ 58,588
Restricted cash, current portion	290	638	193	—
Restricted cash, net of current portion	3,086	290	290	483
Total cash, cash equivalents and restricted cash	$ 44,817	$ 50,814	$ 32,688	$ 59,071

7. Property and Equipment

Property and Equipment consist of the following as of December 31, 2019 and 2018 (in thousands):

	Estimated useful life (in years)	December 31, 2019	December 31, 2018
Construction-in-process	-	$ 164	$ —
Laboratory equipment	5	5,401	4,926
Computer equipment	3	1,628	1,080
Furniture and fixtures	4	852	440
Leasehold improvements	*	11,607	2,717
		$ 19,652	$ 9,163
Less: Accumulated depreciation		(4,442)	(5,302)
Total property and equipment, net		$ 15,210	$ 3,861

* Leasehold improvements are depreciated over the shorter of the life of the asset and the term of the lease at 10.3 years and 5 years as of December 31, 2019 and 2018, respectively. The Company moved into its new corporate headquarters in November 2019 and 10.3 years represents the period until the 2019 Lease expires.

Depreciation expense, including depreciation expense for two immaterial capital leases, for the years ended December 31, 2019, 2018 and 2017 was $2.5 million, $1.6 million and $1.5 million, respectively. Prior to the adoption of ASC 842, office equipment included assets recorded under capital leases of approximately $0.1 million for the year ended December 31, 2018.

8. Accrued Expenses

Accrued expenses consist of the following as of December 31, 2019 and 2018 (in thousands):

	December 31, 2019	December 31, 2018
External research and preclinical development	$ 5,395	$ 10,119
Employee compensation and benefits	4,174	2,985
Professional fees	694	618
Facilities and other	383	171
	$ 10,646	$ 13,893

9. Commitments and Contingencies

Operating Leases

In March 2015, the Company entered into an operating lease for approximately 21,488 rentable square feet of office and laboratory space in Cambridge, Massachusetts (the "2015 Lease"), with a lease term commencing in August 2015 and ending in October 2020. The 2015 Lease had escalating rent payments and the Company recorded rent expense on a straight-line basis over its term, including any rent-free periods. The 2015 Lease included certain lease incentives in the form of tenant allowances. Prior to the adoption of ASC 842, the Company capitalized these improvements made with the tenant allowance into fixed assets and established a liability for the deferred lease incentive upon occupancy. The Company recorded these incentives as a component of deferred rent and amortized these incentives as a reduction of rent expense over the lease term. The related fixed assets were amortized over the expected lease term. Effective January 1, 2019, upon the adoption of ASC 842, the Company recorded a right-of use asset and lease liability of $1.5 million and $2.2 million, respectively, with the remaining deferred rent and tenant allowance incentive included as an offsetting balance within the right-of-use asset

On November 1, 2019, the Company entered into an early termination with the landlord for the 2015 Lease. Pursuant to the termination agreement, the 2015 Lease terminated December 31, 2019, rather than on October 31, 2020 as contemplated by the 2015 Lease.

The Company reviewed the early termination of the 2015 Lease under ASC 842 and determined the early termination resulted in a modification to the 2015 Lease. The Company remeasured the right-of-use asset and lease liability as of the November 1, 2019 modification date, resulting in a lease liability and right-of-use asset of $0.2 million and recorded a $0.1 million gain as result of the modification, which is included in loss from continuing operations. As of December 31, 2019, the 2015 Lease had terminated and all obligations relating the 2015 Lease were satisfied in full with no remaining balances as of that date.

On January 8, 2019, the Company entered into a lease (the "2019 Lease") with respect to approximately 52,859 square feet of space in Cambridge, Massachusetts for a lease term commencing in January 2019 and ending in February 2030. The Company has the option to extend the lease term for one additional ten (10) year period. The 2019 Lease has escalating rent payments and the Company records rent expense on a straight-line basis over the term of the 2019 Lease, including any rent-free periods. The 2019 Lease includes certain lease incentives in the form of tenant allowances. The 2019 Lease also includes an abatement period in which the Company is not required to remit monthly rent payments until March 2020.

In connection with the execution of the 2019 Lease, the Company was required to provide the landlord with a letter of credit in the amount of $3.1 million (See Note 6).

The Company determined that, for purposes of applying ASC 842, the commencement date of the 2019 Lease occurred on May 1, 2019. The Company recorded a right-of-use asset and lease liability of $15.8 million using an incremental borrowing rate of 9.3%, net of tenant allowances expected to be received of $9.3 million, on the May 1, 2019 lease commencement date. The Company is amortizing the tenant allowance to offset rent expenses over the term of the 2019 Lease starting at the lease commencement date on a straight-line basis. On the Company's consolidated balance sheets, the Company classified $1.0 million of the lease liability as short-term and $24.0 million of the lease liability as long-term as of December 31, 2019.

The Company elected the practical expedient provided under ASC 842 and therefore has combined all lease and non-lease components when determining the right-of-use asset and lease liability for the 2019 Lease.

Financing Leases

In March 2019, the Company entered into an equipment lease agreement (the "Equipment Lease") that has a 48-month term. At the end of the term, the Company has the right to return the leased equipment, extend the lease, or buy the equipment at the then-current fair market value of the equipment. The Company accounted for the Equipment Lease as a financing lease under ASC 842 and recorded a financing lease right-of-use asset and a corresponding financing lease liability of approximately $1.0 million at the time of executing the Equipment Lease.

The following is a maturity analysis of the annual undiscounted cash flows reconciled to the carrying value of the operating and financing lease liabilities as of December 31, 2019 (in thousands):

	Operating	Financing
Year ended December 31, 2020	$ 3,122	$ 313
Year ended December 31, 2021	3,824	313
Year ended December 31, 2022	3,935	313
Year ended December 31, 2023	4,049	65
Year ended December 31, 2024 and beyond	27,709	—
Total minimum lease payments	$ 42,639	$ 1,004
Less imputed interest	15,955	142
Less leasehold incentive	1,629	—
Total lease liability	$ 25,055	$ 862

The following table outlines the total lease cost for the Company's operating and financing leases as well as weighted average information for these leases as of December 31, 2019 (in thousands):

	Year Ended December 31, 2019
Lease cost:	
Operating lease cost	$ 2,639
Financing lease cost:	
Amortization of right-of-use asset	$ 201
Interest on lease liabilities	72
Total financing lease cost	$ 273
Cash paid for amounts included in the measurement of liabilities	
Operating cash flows from operating leases	$ 1,346
Operating cash flows from financing lease	$ 277

Other information:	Year Ended December 31, 2019
Weighted-average remaining lease term (in years) - operating lease	10.18
Weighted-average discount rate - operating lease	9.30%
Weighted-average remaining lease term (in years) - financing lease	3.30
Weighted-average discount rate - financing lease	9.47%

Prior to the adoption of ASC 842 effective January 1, 2019, the Company accounted for its leases under the guidance of ASC 840 as either operating with the liability recorded to the balance sheet based on escalating rent payments or capital and recorded to fixed assets and amortized over the term of the lease.

As of December 31, 2018, the Company recorded $0.4 million as deferred rent, current portion and $0.4 million as deferred rent net of current portion, all of which was attributable to our 2015 Lease.

The Company recorded rent expense of $0.9 million for each of the years ended December 31, 2018 and 2017 related to the 2015 Lease.

License Agreements

TMRC Co. Ltd.

In September 2015, the Company entered into an exclusive license agreement with TMRC Co. Ltd. ("TMRC") to develop and commercialize tamibarotene in North America and Europe for the treatment of cancer. This agreement was amended and restated in April 2016.

In exchange for this license, the Company agreed to a non-refundable upfront payment of $1.0 million, for which $0.5 million was paid in September 2015 upon execution of the agreement, and the remaining $0.5 million was paid in May 2016. Under the agreement, the Company is also obligated to make payments upon the successful achievement of clinical and regulatory milestones totaling approximately $13.0 million per indication, defined as a distinct tumor type. In September 2016, the Company paid $1.0 million to TMRC for a development milestone achieved upon the successful dosing of the first patient in its Phase 2 clinical trial of SY-1425. In addition, the Company is obligated to pay TMRC a single-digit percentage royalty, on a country-by-country and product-by-product basis, on net product sales of SY-1425 using know-how and patents licensed from TMRC in North America and Europe for a defined royalty term.

The Company also entered into a supply management agreement with TMRC under which the Company agreed to pay TMRC a fee for each kilogram of SY-1425 active pharmaceutical ingredient that is produced. No payments were made under the supply management agreement during the years ended December 31, 2019 and 2018.

Litigation

The Company is not party to any litigation and does not have contingency reserves established for any litigation liabilities as of December 31, 2019 or December 31, 2018.

10. Convertible Preferred Stock and Warrants

Concurrent Public Offerings and Accounting Treatment

On April 9, 2019, the Company completed two concurrent underwritten public offerings of its equity securities. In the first public offering, the Company sold 8,667,333 shares of its common stock and accompanying Class A warrants (the "Warrants") to purchase 1,951,844 shares of the Company's common stock, at a combined price to the public of $7.50 per common share and accompanying Warrant. In the second public offering, the Company sold 666 shares of its Series A convertible preferred stock (the "Series A Preferred Stock"), and accompanying Warrants to purchase 166,500 shares of the Company's common stock, at a combined public offering price of $7,500 per share and accompanying Warrant. The offerings resulted in aggregate gross proceeds to the Company of $70.0 million, before underwriting discounts and commissions and offering expenses payable by the Company of approximately $5.0 million.

In November 2019, all 666 shares of Series A Preferred Stock were converted to 666,000 shares of common stock. As of December 31, 2019, there were no shares of our Series A Preferred Stock outstanding.

Each Warrant has an exercise price per share of common stock of $8.625, subject to adjustment in certain circumstances, and will expire on October 10, 2022. Each Warrant is immediately exercisable, provided that the holder is prohibited, subject to certain exceptions, from exercising the Warrant for shares of the Company's common stock to the extent that immediately prior to or after giving effect to such exercise, the holder, together with its affiliates and other attribution parties, would own more than 4.99% of the total number of shares of the Company's common stock then issued and outstanding. This percentage may be changed at the holders' election to a higher or lower percentage upon 61 days' notice to the Company.

The Company evaluated the Series A Preferred Stock and Warrants for liability or equity classification in accordance with the provisions of ASC 480, *Distinguishing Liabilities from Equity*, and determined that equity treatment was appropriate because neither the Series A Preferred Stock nor the Warrants met the definition of liability instruments.

The Series A Preferred Stock was not mandatorily redeemable and did not embody an obligation to buy back the shares outside of the Company's control in a manner that could require the transfer of assets. Additionally, the Company determined that the Series A Preferred Stock would be recorded as permanent equity, not temporary equity, given that the holders of equally and more subordinated equity would be entitled to receive the same form of consideration upon the occurrence of the event that gives rise to the redemption or events of redemption that are within the control of the Company.

Additionally, as the effective conversion price of the Series A Preferred Stock of $6.57 was below the fair value of the Company's common stock on the date of issuance of $7.50, the Company determined that the Series A Preferred Stock included a beneficial conversion feature. The Company calculated the beneficial conversion feature to be approximately $0.6 million, which was recorded as a discount to the Series A Preferred Stock at the time of issuance.

The Warrants are classified as a component of permanent equity because they are freestanding financial instruments that are legally detachable and separately exercisable from the shares of common stock with which they were issued, are immediately exercisable, do not embody an obligation for the Company to repurchase its shares, and permit the holders to receive a fixed number of shares of common stock upon exercise. In addition, the Warrants do not provide any guarantee of value or return. The Company valued the Warrants at issuance using the Black-Scholes option pricing model and determined the fair value of the Warrants to purchase 2,118,344 shares of the Company's common stock at $9.0 million. The key inputs to the valuation model included an average volatility of 86.06% and an expected term of 3.5 years.

As of December 31, 2019, Warrants to purchase 2,118,094 shares of common stock are outstanding and remain unexercised.

11. Stock-Based Payments

2016 Stock Incentive Plan

The 2016 Stock Incentive Plan (the "2016 Plan") was adopted by the board of directors on December 15, 2015, approved by the stockholders on June 17, 2016, and became effective on July 6, 2016 upon the closing of the Company's initial public offering ("IPO"). The 2016 Plan replaced the 2012 Equity Incentive Plan (the "2012 Plan"). Any options or awards outstanding under the 2012 Plan remained outstanding and effective. Under the 2016 Plan, the Company may grant incentive stock options, non-statutory stock options, stock appreciation rights, restricted stock, restricted stock units and other stock-based awards. The number of shares of the Company's common stock reserved for issuance under the 2016 Plan automatically increases on the first day of each calendar year, through the 2025 calendar year, in an amount equal to the least of (i) 1,600,000 shares of common stock, (ii) 4.0% of the outstanding shares of common stock as of such date, or (iii) such lesser amount as specified by the board of directors. This number is subject to adjustment in the event of a stock split, stock dividend or other change in the Company's capitalization. For the calendar year beginning January 1, 2019, the number of shares reserved for issuance under the 2016 Plan was increased by 1,350,634 shares. At December 31, 2019, 2,125,238 shares remained available for future issuance under the 2016 Plan. Under the 2016 Plan, stock options may not be granted at less than fair value on the date of grant.

2016 Employee Stock Purchase Plan

The 2016 Employee Stock Purchase Plan (the "2016 ESPP") was adopted by the board of directors on December 15, 2015, approved by the stockholders on June 17, 2016, and became effective on July 6, 2016 upon the closing of the IPO. The number of shares of the Company's common stock reserved for issuance under the 2016 ESPP automatically increases on the first day of each calendar year through the 2025 calendar year, in an amount equal to the least of (i) 1,173,333 shares of the Company's common stock, (ii) 1.0% of the total number of shares of the Company's common stock outstanding on the first day of the applicable year, and (iii) an amount determined by the Company's board of directors. For the calendar year beginning January 1, 2019, the number of shares reserved for issuance under the 2016 ESPP was increased by 337,658 shares. At December 31, 2019, 1,395,028 shares remained available for future issuance under the 2016 ESPP.

Stock Options

Terms of stock option agreements, including vesting requirements, are determined by the board of directors, subject to the provisions of the 2016 Plan. Stock option awards granted by the Company generally vest over four years, with 25% vesting on the first anniversary of the vesting commencement date and 75% vesting ratably, on a monthly basis, over the remaining three years. Such awards have a contractual term of ten years from the grant date.

The Company has granted stock options to management for which vesting accelerates upon the achievement of performance-based criteria. Milestone events are specific to the Company's corporate goals, including but not limited to certain clinical development milestones and the Company's ability to execute on its corporate development and financing strategies. Stock-based compensation expense associated with these performance-based stock options is recognized based on the accelerated attribution model. Management evaluates when the achievement of a performance-based milestone is probable based on the expected satisfaction of the performance conditions as of the reporting date. Notwithstanding any vesting in accordance with the achievement of performance-based milestones, such awards vest in full on the sixth anniversary of the vesting commencement date. During the years ended December 31, 2019 and 2018, the Company recorded additional stock-based compensation expense of $0.4 million and $0.2 million, respectively, related to the acceleration of vesting of certain stock options associated with the entry into the GBT Collaboration Agreement in December 2019 and Incyte Collaboration Agreement in February 2018, respectively. As of December 31, 2019, there was $0.4 million of unrecognized stock-based compensation expense related to the performance-based stock options granted to management, with an expected recognition period of 2.9 years.

The Company has granted options to purchase 75,000 shares of common stock to an advisor that vest solely upon the achievement of performance-based criteria. As of December 31, 2019, none of these performance-based criteria had been achieved. As of December 31, 2019, there was $0.3 million of unrecognized compensation cost related to this option, with a remaining contractual period of 6.7 years.

A summary of the status of stock options as of December 31, 2019 and December 31, 2018 and changes during the year ended December 31, 2019 is presented below:

	Shares	Weighted Average Exercise Price	Remaining Contractual Life (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding at December 31, 2018	3,732,643	$ 9.88	7.9	$ 1,694
Granted	1,175,500	6.68		
Exercised	(60,181)	3.48		
Cancelled	(229,541)	9.55		
Outstanding at December 31, 2019	4,618,421	$ 9.16	7.5	$ 2,525
Exercisable at December 31, 2019	2,407,267	$ 9.41	6.6	$ 2,190

The intrinsic value of stock options exercised during the years ended December 31, 2019, 2018 and 2017 was $0.2 million, $1.4 million and $4.6 million, respectively.

As of December 31, 2019, there was $12.0 million of total unrecognized compensation cost related to non-vested stock options granted to employees, excluding those stock option grants subject to the achievement of performance milestones, which is expected to be recognized over a weighted-average period of 2.6 years.

Cash received from option exercises during the years ended December 31, 2019, 2018, and 2017 was $0.2 million, $0.6 million, and $1.8 million, respectively.

Restricted Stock Units

From time to time, upon approval by the Company's board of directors, certain employees have been granted restricted stock units with time-based vesting criteria. The majority of these restricted stock units vest annually over a four-year term with 25% vesting on each anniversary of the grant date. Restricted stock units granted to the Company's executive officers vest in full three-years from the date of grant. The fair value of restricted stock units is calculated based on the closing sale price of the Company's common stock on the date of grant.

A summary of the status of restricted stock units as of December 31, 2018 and December 31, 2019 and changes during the year ended December 31, 2019 is presented below:

	Shares	Weighted Average Grant Date Fair Value
Outstanding at December 31, 2018	—	$ —
Granted	1,168,424	6.75
Vested	—	—
Forfeited	(52,066)	6.71
Outstanding at December 31, 2019	1,116,358	$ 6.75

As of December 31, 2019, there was $5.7 million of unrecognized stock-based compensation expense related to outstanding restricted stock units, with an expected recognition period of 2.7 years.

Stock-based Compensation Expense

The fair value of each stock option granted was estimated on the date of grant using the Black-Scholes option-pricing model based on the following weighted-average assumptions:

	Year Ended December 31,		
	2019	2018	2017
Weighted-average risk-free interest rate	2.42 %	2.56 %	2.07 %
Expected dividend yield	— %	— %	— %
Expected option term (in years)	6.00	6.04	6.05
Volatility	91.35 %	90.26 %	87.83 %

The weighted-average grant date fair value per share of options granted in the years ended December 31, 2019, 2018 and 2017 was $5.05, $7.80 and $8.75, respectively.

The following table summarizes the stock-based compensation expense for stock options, restricted stock units and restricted common stock granted to employees and non-employees and from the 2016 ESPP recorded in the Company's statements of operations:

	Year Ended December 31,		
	2019	2018	2017
Research and development	$ 3,472	$ 2,412	$ 1,666
General and administrative	6,367	4,198	2,753
Total stock-based compensation expense	$ 9,839	$ 6,610	$ 4,419

Due to an operating loss, the Company does not record tax benefits associated with stock-based compensation or option exercises. Tax benefits will be recorded when realized.

12. Income Taxes

The Company accounts for income taxes under FASB Accounting Standards Codification 740 ("ASC 740"). Deferred income tax assets and liabilities are determined based upon differences between financial reporting and tax bases of assets and liabilities and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. The components of the income tax provision for the years ended December 31, 2019, 2018 and 2017 are as follows:

	Year Ended December 31,		
	2019	2018	2017
Current	$ 28	$ 24	$ 7
Deferred	—	—	—
Total	$ 28	$ 24	$ 7

A reconciliation of the U.S. statutory income tax rate to the Company's effective tax rate is as follows for the years ended December 31, 2019, 2018 and 2017:

	Year ended December 31,		
	2019	2018	2017
Federal income tax computed at federal statutory tax rate	21.00 %	21.00 %	34.00 %
State income tax, net of federal benefit	6.56	6.01	5.35
Permanent items	(0.89)	(0.61)	(1.57)
Federal and state research and development credits	4.79	4.79	7.36
Rate change	—	—	(31.79)
Other	(0.77)	0.01	0.66
Change in valuation allowance	(30.73)	(31.24)	(14.02)
Effective income tax rate	(0.04)%	(0.04)%	(0.01)%

The principal components of the Company's deferred tax assets and liabilities consist of the following at December 31, 2019 and 2018 (in thousands):

	Year ended December 31,	
	2019	2018
Deferred tax assets:		
Federal and state net operating loss carryforwards	$ 68,026	$ 51,346
Tax credit carryforwards	14,170	10,558
Intangible assets	46	51
Stock-based compensation	3,774	2,108
Leasehold incentive	—	155
Deferred revenue	2,289	—
Capital lease	7,526	—
Other	1,432	2,809
Total deferred tax assets	97,263	67,027
Less valuation allowance	(90,198)	(67,027)
Net deferred tax assets	7,065	—
Deferred tax liabilities:		
Right-of-use asset	4,557	—
Fixed assets	2,508	—
Total deferred tax liabilities	7,065	—
Net deferred taxes	$ —	$ —

As of December 31, 2019, the Company had federal net operating loss ("NOL") carryforwards of approximately $248.2 million and state net operating loss carryforwards of $251.7 million which are available to reduce future taxable income. The Company also had federal tax credits of approximately $11.9 million and state tax credits of $2.9 million which may be used to offset future tax liabilities. Net operating losses generated before 2018 of approximately $135.7 million will expire at various dates through 2037, and net operating losses of approximately $112.5 million, which were generated after 2017 have an indefinite carryforward period. The NOL and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service and state tax authorities. Net operating loss and tax credit carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders over a three-year period in excess of 50%, as defined under Sections 382 and 383 of the Internal Revenue Code, respectively, as well as similar state provisions. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of the Company immediately prior to the ownership change. Subsequent ownership changes may further affect the limitation in future years. The Company has not determined whether an ownership change has occurred and as such, the Company's NOLs may be limited.

ASC 740 requires a valuation allowance to reduce the deferred tax assets reported if, based on the weight of the evidence, it is more likely than not that some portion or all of the deferred tax assets will not be realized. After consideration of all the evidence, both positive and negative, the Company has recorded a valuation allowance against its deferred tax assets at December 31, 2018 and 2019, respectively because the Company's management has determined that it is more likely than not that these assets will not be fully realized. The increase in the valuation allowance of $23.2 million in 2019 and $19.5 million in 2018 primarily relates to the net loss incurred by the Company.

The Company's reserves related to taxes are based on a determination of whether and how much of a tax benefit taken by the Company in its tax filings or positions is more likely than not to be realized following resolution of any potential contingencies present related to the tax benefit. As of December 31, 2019 and 2018 the Company had no unrecognized tax benefits or accrued interest or penalties related to unrecognized tax benefits. The Company's policy is to recognize both interest and penalties related to unrecognized tax benefits in income tax expense.

The Company completed a study to document its qualifying research credits for all years except the years ended December 31, 2018 and 2019. For the years ended December 31, 2018 and 2019, the Company generated research credits but has not conducted a study to document the qualified activities. This study may result in an adjustment to the Company's research and development credit carryforwards; however, until a study is completed and any adjustment is known, no amounts are being presented as an unrecognized tax benefit for the years ended December 31, 2018 and 2019. A full valuation allowance has been provided against the Company's research and development credits and, if an adjustment is required, this adjustment would be offset by an adjustment to the deferred tax asset established for the research and development credit carryforwards and the valuation allowance.

The federal and state income tax returns are generally subject to examinations for the tax years ended December 31, 2016 through December 31, 2019. To the extent the Company has tax attribute carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by the Internal Revenue Service or state tax authorities to the extent utilized in a future period. The Company files income tax returns in the U.S. federal and Massachusetts jurisdictions. There are currently no federal or state audits in process.

13. Defined Contribution Plan

The Company established a defined contribution savings plan under Section 401(k) of the Internal Revenue Code. This plan covers substantially all employees who meet minimum age and service requirements and allows participants to defer a portion of their annual compensation on a pretax or post-tax basis. Company contributions to the plan may be made at the discretion of the board of directors. The Company instituted effective September 1, 2017 an employer match of 100% of the amount the employees contribute to the 401(k) plan for each payroll period up to the first 1% of plan compensation plus 50% of the amount the employees contribute between 1% and 6% of plan compensation. For the years ended December 31, 2019, 2018, and 2017 the Company contributed $0.5 million, $0.4 million and $0.3 million respectively, to the 401(k) plan.

14. Subsequent Events

On February 12, 2020, the Company entered into a Loan and Security Agreement (the "Loan Agreement") by and among the Company and Oxford Finance LLC, in its capacity as lender (in such capacity, the "Lender"), and in its capacity as collateral agent (in such capacity, the "Agent"), pursuant to which a term loan of up to an aggregate principal amount of $60.0 million is available to the Company. A $20.0 million term loan was funded on the closing date, and two additional term loan advances of $20.0 million each will be available under the Loan Agreement after the closing date, subject to certain terms and conditions, including the achievement of certain milestones.

The term loans bear interest at an annual rate equal to the greater of (i) 7.75% and (ii) the sum of 5.98% and the greater of (A) one-month LIBOR and (B) 1.77%. The Loan Agreement provides for interest-only payments until March 1, 2023, and repayment of the aggregate outstanding principal balance of the term loan in monthly installments starting on March 1, 2023 and continuing through February 1, 2025 (the "Maturity Date"). The Company paid a facility fee of $100,000 upon closing, and in addition will pay a facility fee of $75,000 upon closing of the second loan tranche and a $50,000 facility fee upon the closing of the third loan tranche. The Company will be required to make a final payment fee of 5.00% of the amount of the term loan drawn payable on the earlier of (i) the prepayment of the term loan or (ii) the Maturity Date. At the Company's option, the Company may elect to prepay the loans subject to a prepayment fee equal to the following percentage of the principal amount being prepaid: 2% if an advance is prepaid during the first 12 months following the applicable advance date, 1% if an advance is prepaid after 12 months but prior to 24 months following the applicable advance date, and 0.5% if an advance is prepaid any time after 24 months following the applicable advance date but prior to the Maturity Date.

In connection with the Loan Agreement, the Company granted the Agent a security interest in all of the Company's personal property now owned or hereafter acquired, excluding intellectual property (but including the right to payments and proceeds of intellectual property), and a negative pledge on intellectual property. The Loan Agreement also contains certain events of default, representations, warranties and non-financial covenants of the Company.

In addition, under the Loan Agreement, the Company issued the Lender warrants to purchase 27,548 shares of the Company's common stock at an exercise price per share of $7.26 (the "Oxford Warrants"). The Oxford Warrants will be exercisable for five years from the date of issuance.

15. Selected Quarterly Financial Data (unaudited)

The following table contains selected quarterly financial information for 2019 and 2018. The Company believes that the following information reflects all normal recurring adjustments necessary for a fair statement of the information for the periods presented. The operating results for any quarter are not necessarily indicative of results for any future period.

	Three Months Ended			
	March 31, 2019	June 30, 2019	September 30, 2019	December 31, 2019
Revenue	$ 454	$ 462	$ 558	508
Operating expenses:				
Research and development	12,562	15,475	15,931	14,277
General and administrative	4,865	5,195	5,016	6,402
Total operating expenses	17,427	20,670	20,947	20,679
Loss from operations	(16,973)	(20,208)	(20,389)	(20,171)
Other income, net	512	753	596	442
Net loss applicable to common stockholders	$ (16,461)	$ (19,455)	$ (19,793)	(19,729)
Net loss per share applicable to common stockholders - basic and diluted	$ (0.49)	$ (0.47)	$ (0.47)	(0.46)
Weighted-average number of common shares used in net loss per share applicable to common stockholders - basic and diluted	33,766,333	41,673,275	42,439,338	42,885,208

	Three Months Ended			
	March 31, 2018	June 30, 2018	September 30, 2018	December 31, 2018
Revenue	$ 370	$ 375	$ 412	$ 893
Operating expenses:				
Research and development	11,116	11,082	12,856	15,128
General and administrative	4,075	3,841	3,876	4,372
Total operating expenses	15,191	14,923	16,732	19,500
Loss from operations	(14,821)	(14,548)	(16,320)	(18,607)
Other income, net	358	501	583	575
Net loss applicable to common stockholders	$ (14,463)	$ (14,047)	$ (15,737)	$ (18,032)
Net loss per share applicable to common stockholders - basic and diluted	$ (0.48)	$ (0.43)	$ (0.47)	$ (0.54)
Weighted-average number of common shares used in net loss per share applicable to common stockholders - basic and diluted	30,335,164	32,892,712	33,653,479	33,694,756

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A. CONTROLS AND PROCEDURES

Management's Evaluation of Disclosure Controls and Procedures

We maintain "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act, that are designed to ensure that information required to be disclosed in the reports that we file or submit under the Exchange Act is (1) recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms and (2) accumulated and communicated to our management, including our principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Our 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. Our disclosure controls and procedures are designed to provide reasonable assurance of achieving their control objectives.

Our management, with the participation of our Chief Executive Officer, who serves as our principal executive officer, and our Chief Financial Officer, who serves as our principal financial officer, has evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2019, the end of the period covered by this Annual Report on Form 10-K. Based upon such evaluation, our chief executive officer and chief financial officer have concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of such date.

Internal Control Over Financial Reporting

Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over our financial reporting. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, our principal executive and principal financial officers and effected by our board of directors, management and other personnel to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with U.S. GAAP. Our internal control over financial reporting includes those policies and procedures that:

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

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

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

This Annual Report on Form 10-K does not include an attestation report of our independent registered public accounting firm regarding internal control over financial reporting due to an exemption established by the Jumpstart Our Business Startups Act of 2012 for "emerging growth companies."

Changes in Internal Control Over Financial Reporting

Effective January 1, 2019, we adopted the provisions of ASC 842, *Leases*. As part of the adoption of this standard, we reviewed our control procedures and have modified certain of our processes to ensure compliance with the new standard.

Other than the foregoing, during the year ended December 31, 2019, there were no other changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

The information set forth below is included herein for the purpose of providing the disclosure required under "Item 5.02 – Departure of Directors or Certain Officers; Election of Directors; Appointment of Certain Officers; Compensatory Arrangements of Certain Officers" of Form 8-K.

In September 2019, Bristol-Myers Squibb Company, or BMS, announced that Michael W. Bonney would be joining its board of directors following completion of its acquisition of Celgene Corporation and, in connection therewith, Mr. Bonney committed to comply by the end of the first quarter of 2020 with BMS's policy that directors not serve on more than four public company boards of directors. On March 3, 2020, Mr. Bonney informed us of his decision to resign from our board of directors with immediate effect. This resignation was not the result of any disagreement with our company.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by this Item 10 will be included under the captions "Executive Officers," "Election of Directors" and "Delinquent Section 16(a) Reports," if applicable, in our definitive proxy statement to be filed with the SEC with respect to our 2020 Annual Meeting of Stockholders and is incorporated herein by reference.

We have adopted a Code of Business Conduct and Ethics that applies to our officers, including our principal executive, financial and accounting officers, and our directors and employees. We have posted the text of our Code of Business Conduct and Ethics under the "News & Investors— Corporate Governance" section of our website, *www.syros.com*. We intend to disclose on our website any amendments to, or waivers from, the Code of Business Conduct and Ethics that are required to be disclosed pursuant to the disclosure requirements of Item 5.05 of Form 8-K.

ITEM 11. EXECUTIVE COMPENSATION

The information required by this Item 11 will be included under the captions "Executive and Director Compensation" and "Compensation Committee Interlocks and Insider Participation" in our definitive proxy statement to be filed with the SEC with respect to our 2020 Annual Meeting of Stockholders and is incorporated herein by reference.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERSHIP AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required by this Item 12 will be included under the captions "Security Ownership of Certain Beneficial Owners and Management" and "Securities Authorized for Issuance Under Equity Compensation Plans" in our definitive proxy statement to be filed with the SEC with respect to our 2020 Annual Meeting of Stockholders and is incorporated herein by reference.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The information required by this Item 13 will be included, as applicable, under the captions "Employment Agreements," "Potential Payments Upon Termination or Change in Control," "Board Determination of Independence" and "Related Person Transactions" in our definitive proxy statement to be filed with the SEC with respect to our 2020 Annual Meeting of Stockholders and is incorporated herein by reference.

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES

The information required by this Item 14 will be included under the captions "Audit Fees and Services" and "Pre-Approval Policies and Procedures" in our definitive proxy statement to be filed with the SEC with respect to our 2020 Annual Meeting of Stockholders and is incorporated herein by reference.

PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

(a) *Financial Statements*

For a list of the consolidated financial statements included herein, see Index to the Consolidated Financial Statements on page 102 of this Annual Report on Form 10-K, which is incorporated into this Item by reference.

(b) *Exhibits*

		Incorporation by Reference			
Exhibit No.	Description	Form	SEC Filing Date	Exhibit Number	Filed with this 10-K
Organizational Documents and Documents Related to Common Stock					
3.1	Restated Certificate of Incorporation of the Registrant, including the Certificate of Designation of Preferences, Rights and Limitations of Series A Convertible Preferred Stock of the Registrant	8-K	4/8/19	3.1	
3.2	Amended and Restated Bylaws of the Registrant	8-K	7/6/16	3.2	
4.1	Description of Securities Registered under Section 12 of the Exchange Act				X
4.2	Form of Common Stock Certificate	S-1^	6/3/16	4.1	
4.3	Form of Class A Warrant	8-K	4/8/19	4.1	
4.4	Form of Series A Convertible Preferred Stock Certificate	8-K	4/8/19	4.2	
4.5	Second Amended and Restated Investors' Rights Agreement dated October 9, 2014, as amended, among the Registrant and the other parties thereto	S-1^	6/3/16	4.2	
4.6	Sales Agreement dated July 20, 2017 by and between the Registrant and Cowen and Company, LLC	S-3^^	7/20/17	1.2	
4.7	Securities Purchase Agreement dated April 20, 2017 by and among the Registrant and the persons party thereto	8-K	4/21/17	10.1	
4.8	Registration Rights Agreement, dated April 20, 2017, by and among the Registrant and the persons party thereto	8-K	4/21/17	10.2	
Equity Plan Documents					
10.1*	2012 Equity Incentive Plan, as amended	S-1^	6/3/16	10.1	
10.2*	Form of Incentive Stock Option Agreement under 2012 Equity Incentive Plan	S-1^	6/3/16	10.2	
10.3*	Form of Nonstatutory Stock Option Agreement under 2012 Equity Incentive Plan	S-1^	6/3/16	10.3	
10.4*	Form of Restricted Stock Agreement under 2012 Equity Incentive Plan	S-1^	6/3/16	10.4	
10.5*	2016 Stock Incentive Plan	S-1^	6/3/16	10.5	
10.6*	Form of Incentive Stock Option Agreement under 2016 Stock Incentive Plan	S-1^	6/3/16	10.6	
10.7*	Form of Nonstatutory Stock Option Agreement under 2016 Stock Incentive Plan	S-1^	6/3/16	10.7	
10.8*	Form of Restricted Stock Unit Agreement under 2016 Stock Incentive Plan	10-K	3/7/19	10.8	
10.9*	2016 Employee Stock Purchase Plan	S-1^	6/3/16	10.8	
Agreements with Directors and Executive Officers					
10.10*	Offer Letter, dated November 13, 2012 and effective as of July 2, 2012 by and between the Registrant and Nancy Simonian, M.D., as amended	S-1^	6/3/16	10.9	
10.11*	Offer Letter dated December 2, 2015 by and between the Registrant and David A. Roth, M.D., as amended	S-1^	6/3/16	10.11	
10.12*	Offer Letter dated November 6, 2017 by and between the Registrant and Jeremy Springhorn, Ph.D.	10-K	3/12/18	10.13	
10.13*	Offer Letter effective March 12, 2018 by and between the Registrant and Joseph J. Ferra, Jr.	8-K	3/12/18	10.1	
10.14*	Offer Letter dated April 24, 2013 by and between the Registrant and Eric R. Olson, Ph.D.				X
10.15*	Consulting Agreement dated August 8, 2012 by and between the Registrant and Richard A. Young, Ph.D., as amended	10-Q	11/12/19	10.1	
10.16*	Form of Director and Officer Indemnification Agreement by and between the Registrant and each of the directors and executive officers of the Registrant	S-1^	6/3/16	10.12	

License and Collaboration Agreements					
10.17+	Amended and Restated Cancer License Agreement dated April 28, 2016 by and between the Registrant and TMRC Co., Ltd.	10-K	3/7/19	10.16	
10.18+	Supply Management Agreement dated April 28, 2016 by and between the Registrant and TMRC Co., Ltd.	S-1^	6/3/16	10.18	
10.19	Consent and Stand-by License Agreement dated April 28, 2016 by and among the Registrant, Toko Pharmaceutical Ind. Co., Ltd. and TMRC Co., Ltd.	S-1^	6/3/16	10.19	
10.20+	Target Discovery, Research Collaboration and Option Agreement dated January 8, 2018 by and between the Registrant and Incyte Corporation	10-K	3/12/18	10.22	
10.21++	Letter Agreement dated November 18, 2019 by and between the Registrant and Incyte Corporation				X
10.22++	License and Collaboration Agreement dated December 17, 2019 by and between the Registrant and Global Blood Therapeutics, Inc.				X
Leases and Loan Documents					
10.23	Lease dated January 8, 2019 by and between the Registrant and DIV 35 CPD, LLC	8-K	1/11/19	10.1	
10.24	Loan and Security Agreement dated February 12, 2020 by and between the Registrant and Oxford Finance LLC, as collateral agent and lender	8-K	2/13/20	1.1	
Subsidiaries, Consents and Certifications					
21.1	Subsidiaries of the Registrant	10-K	3/7/19	21.1	
23.1	Consent of Ernst & Young LLP, independent public accounting firm				X
31.1	Certification of principal executive officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended				X
31.2	Certification of principal financial officer pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934, as amended				X
32.1#	Statement 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#	Statement 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
XBRL Documents					
101.INS	XBRL Instance Document				
101.SCH	XBRL Taxonomy Extension Schema Document				
101.CAL	XBRL Calculation Linkbase Document				
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document				
101.LAB	XBRL Label Linkbase Document				
101.PRE	XBRL Taxonomy Presentation Linkbase Document				

* Indicates management contract or compensatory plan.
\+ Confidential treatment has been requested and/or granted as to certain portions, which portions have been omitted and filed separately with the U.S. Securities and Exchange Commission.
++ Portions of this exhibit have been omitted pursuant to Item 601(b)(10)(iv) of Regulation S-K.
^ SEC File No. 333-211818
^^ SEC File No. 333-219369
\# This certification will not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liability of that section. Such certification will not be deemed to be incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act, except to the extent specifically incorporated by reference into such filing.

(c) *Financial Statement Schedules*

No financial statement schedules have been submitted because they are not required or are not applicable or because the information required is included in the consolidated financial statements or the notes thereto.

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.

SYROS PHARMACEUTICALS, INC.

Date: March 5, 2020

By: /s/ Nancy Simonian, M.D.
Nancy Simonian, M.D.
President and Chief Executive Officer

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

Signature	Title	Date
/s/ Nancy Simonian, M.D. Nancy Simonian, M.D.	President, Chief Executive Officer and Director (*Principal Executive Officer*)	March 5, 2020
/s/ Joseph J. Ferra, Jr. Joseph J. Ferra, Jr.	Chief Financial Officer (*Principal Financial Officer and Principal Accounting Officer*)	March 5, 2020
/s/ Peter Wirth Peter Wirth	Chair of the Board of Directors	March 5, 2020
/s/ Srinivas Akkaraju, M.D., Ph.D. Srinivas Akkaraju, M.D., Ph.D.	Director	March 5, 2020
/s/ Mark J. Alles Mark J. Alles	Director	March 5, 2020
/s/ Marsha H. Fanucci Marsha H. Fanucci	Director	March 5, 2020
/s/ Amir Nashat, Ph.D. Amir Nashat, Ph.D.	Director	March 5, 2020
/s/ Phillip A. Sharp, Ph.D. Phillip A. Sharp, Ph.D.	Director	March 5, 2020
/s/ Richard A. Young, Ph.D. Richard A. Young, Ph.D.	Director	March 5, 2020

BOARD OF DIRECTORS

Peter Wirth, Chair
Former EVP, Legal and Corporate Development, Genzyme Corporation

Srinivas Akkaraju, M.D., Ph.D.
Managing General Partner, Samsara BioCapital

Mark J. Alles
Former Chairman and CEO, Celgene Corporation

Marsha H. Fanucci
Former Chief Financial Officer, Millennium Pharmaceuticals

Amir Nashat, Ph.D.
Managing Partner, Polaris Venture Partners

Phillip A. Sharp, Ph.D.
Nobel Laureate; Institute Professor, Massachusetts Institute of Technology

Nancy A. Simonian, M.D.
Chief Executive Officer, Syros Pharmaceuticals

Richard A. Young, Ph.D.
Member, Whitehead Institute
Professor of Biology, Massachusetts Institute of Technology

MANAGEMENT TEAM

Nancy A. Simonian, M.D.
Chief Executive Officer

Joseph J. Ferra, Jr.
Chief Financial Officer

Eric R. Olson, Ph.D.
Chief Scientific Officer

Gerald E. Quirk, Esq.
Chief Legal & Administrative Officer

David A. Roth, M.D.
Chief Medical Officer

Jeremy P. Springhorn, Ph.D.
Chief Business Officer

Kristin O. Stephens
Senior Vice President, Product Development

ANNUAL MEETING

The Annual Meeting of Stockholders will be held at 11:30 a.m. EDT on June 11, 2020 at:

Syros Pharmaceuticals, Inc.
35 CambridgePark Drive, 4th Floor
Cambridge, MA 02140

INDEPENDENT AUDITORS

Ernst & Young LLP
Boston, MA

INVESTOR INQUIRIES

Hannah Deresiewicz
Stern Investor Relations, Inc.
212-362-1200
hannah.deresiewicz@sternir.com

STOCK LISTING

NASDAQ: SYRS

TRANSFER AGENT

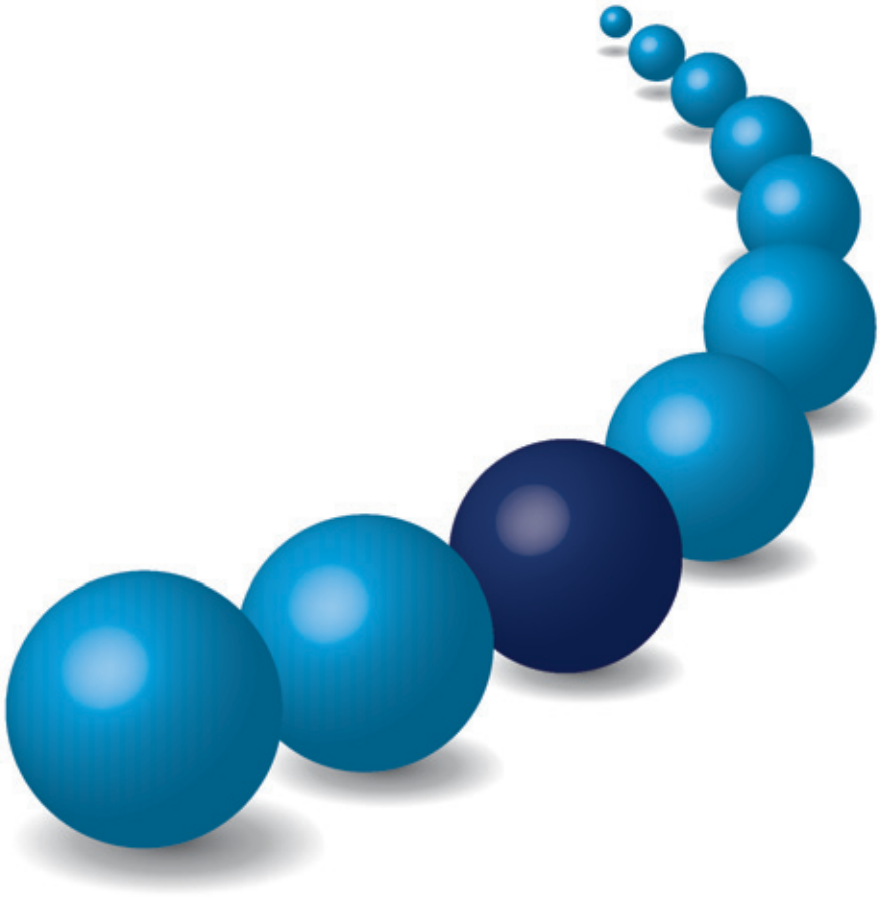
The transfer agent is responsible, among other things, for handling stockholder questions regarding lost stock certificates, address changes, including duplicate mailings, and changes in ownership or name in which shares are held. These requests may be directed to the transfer agent at the following address:

Computershare Trust Company, N.A.
P.O. Box 43078
Providence, RI 02940-3078

SEC FORM 10-K

A copy of Syros' 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 212-362-1200, sending a request by email to hannah.deresiewicz@sternir.com or sending a written request to:

Investor Relations
Syros Pharmaceuticals, Inc.
35 CambridgePark Drive, 4th Floor
Cambridge, MA 02140



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