
SYROS
An expression makes a world of difference
2017
Annual Report

Dear Fellow Shareholders,

At Syros, we are committed to making a difference in the lives of patients with cancer and genetic diseases through our leadership in gene control and our exceptional people and culture. We made great strides toward this vision in 2017, driving our lead program to an initial clinical data readout, advancing our second program into clinical development, and initiating our first program in genetic diseases. We reported the initial data from the Phase 2 clinical trial of SY-1425, our first-in-class selective retinoic acid receptor alpha (RARα) agonist, providing strong support for the ongoing development of SY-1425 as a combination agent in genomically defined subsets of patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). We initiated a Phase 1 clinical trial for our second program, SY-1365, a first-in-class selective cyclin-dependent kinase 7 (CDK7) inhibitor, in patients with advanced solid tumors. We also continued to enhance our leading gene control platform to fuel our pipeline in cancer, including immuno-oncology, as well as to expand into genetic diseases, starting with sickle cell disease, where controlling the expression of a single known gene could provide a significant benefit for patients.

These accomplishments position us for a potentially transformative year in 2018 with clinical data expected for both SY-1425 and SY-1365, the planned selection of a development candidate to support a potential Investigational New Drug application in 2019 to advance a third program into clinical trials, and the continued evolution of our team and capabilities. Already in 2018, we have entered into a collaboration with Incyte Corporation to discover and validate novel drug targets for myeloproliferative neoplasms, leveraging our platform to benefit patients with diseases beyond our current areas of focus. We also completed a $46 million public offering, giving us the capital resources to fund our planned operations into 2020 and to drive SY-1425 and SY-1365 to key value inflection points.

Looking ahead to the rest of the year, we expect to report data in the fourth quarter from two cohorts in the Phase 2 clinical trial of SY-1425 assessing its safety and efficacy in combination with azacitidine, a standard-of-care therapy, in *RARA* and *IRF8* biomarker-positive newly diagnosed AML patients who are not suitable candidates for standard chemotherapy, and in combination with daratumumab, a targeted anti-CD38 therapy, in *RARA* and *IRF8* biomarker-positive relapsed or refractory AML and higher-risk MDS patients. We expect to complete the dose escalation portion of the Phase 1 trial of SY-1365 in the middle of this year and open expansion cohorts evaluating SY-1365 as a single agent and in combination with other drugs in multiple ovarian and breast cancer populations. We plan to report data from the dose escalation portion of the Phase 1 trial in the fourth quarter of this year.

Since our inception, our vision for Syros has been to build a great and sustainable company that translates our leadership in gene control into therapies that provide a profound and durable benefit for patients. The progress we have made toward that vision in just five years is a testament to the quality of our people, the power of our platform and the potential of our programs. I firmly believe the best is yet to come, and I look forward to keeping you updated on our continued progress.

Sincerely,

Nancy 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, 2017

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.)**
620 Memorial Drive, Suite 300 Cambridge, Massachusetts	**02139**
(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	**Name of Exchange on Which Registered**
Common Stock, $0.001 par value	**Nasdaq Global Select Market**

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

None.

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

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

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☑ No ☐

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

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

Large accelerated filer	☐	Accelerated filer	☑
Non-accelerated filer	☐	Smaller reporting company	☐
(Do not check if a 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 30, 2017, 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 $289,542,157, 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 2018 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, 2017, 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 28, 2018, the registrant had 32,193,961 shares of Common Stock, $0.001 par value per share, outstanding.

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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, expand and/or report data from our clinical trials for SY-1425 and SY-1365;
- 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 plans to research, develop, 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;
- the potential benefits of any future collaboration;
- the timing of and our ability to 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;

- our estimates regarding expenses, future revenue, capital requirements and need for additional financing;
- developments relating to our competitors and our industry; and
- the impact of government laws and regulations.

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.

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 pioneering an understanding of the non-coding regulatory region of the genome controlling the activation and repression of genes. Our goal is to advance a new wave of medicines to control the expression of genes. We have built a proprietary gene control platform designed to systematically and efficiently analyze this unexploited region of DNA in human disease tissue to identify novel targets linked to genomically defined patient populations and to develop drugs against those targets based on our expertise in transcriptional chemistry. Because gene expression is fundamental to the function of all cells, we believe that our gene control platform has broad potential to create medicines that achieve profound and durable benefit across therapeutic areas and a range of diseases. We are currently focused on developing treatments for cancer and diseases resulting from modifications of a single gene, also known as monogenic diseases, and are 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 being evaluated in combination with azacitidine, a hypomethylating agent frequently used to treat acute myeloid leukemia, or AML, and myelodysplastic syndrome, or MDS, patients, and with daratumumab, an anti-CD38 therapeutic antibody approved to treat multiple myeloma, in a Phase 2 clinical trial in genomically defined subsets of patients with AML and MDS; and

- SY-1365, a selective inhibitor of cyclin-dependent kinase 7, or CDK7, in a Phase 1 clinical trial in patients with advanced solid tumors for which expansions in ovarian and breast cancer are planned.

We also have multiple programs in earlier stages of research and development in oncology, including immuno-oncology, and monogenic diseases. Our goal is to build a fully integrated biopharmaceutical company based on our leadership position in gene control.

At the 59th American Society of Hematology Annual Meeting and Exposition in December 2017, or ASH 2017, we presented clinical data from our Phase 2 clinical trial evaluating SY-1425 as a single agent in defined subsets of AML and MDS patients with our proprietary *RARA* and *IRF8* biomarkers. In 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 and that clinical and biological activity was observed in patients enrolled in the trial. Specifically, clinical activity was observed in ten of 23 (43%) evaluable patients with relapsed or refractory AML and higher-risk MDS, including improvement in blood counts, reduction in leukemic blasts and one bone marrow complete response. Thirteen of the 23 (57%) evaluable relapsed or refractory AML and higher-risk MDS patients had stable disease. Myeloid differentiation was also observed in the bone marrow, consistent with the underlying mechanism of action of SY-1425 as a differentiating agent. Induction of CD38, a marker of cell differentiation, was observed after one 28-day cycle of treatment in 11 of 13 (85%) patients with pre- and post-treatment immunophenotyping samples.

We believe that these clinical data, when combined with preclinical data showing the tumor-killing activity of SY-1425 in combination with azacitidine and with daratumumab, support the ongoing development of SY-1425 as a combination agent. SY-1425 has shown synergistic tumor-killing activity in combination with azacitidine as well as with daratumumab in preclinical models of *RARA* biomarker-positive AML. In combination with azacitidine, SY-1425 demonstrated greater clearance of tumor cells in bone marrow and other tissues and greater depth and duration of tumor response in preclinical models, compared to either azacitidine or SY-1425 alone. In combination with daratumumab, SY-1425 induced robust immune cell-mediated tumor death *in vitro*. Notably, AML cells do not normally express high levels of CD38. We have shown that by inducing CD38 expression, SY-1425 sensitizes biomarker-positive AML models to the tumor-killing effects of daratumumab.

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 not suitable candidates for standard chemotherapy, and in combination with daratumumab in approximately 12 relapsed or refractory AML and higher-risk MDS patients. All patients enrolled or to be enrolled in the trial have been or will be prospectively selected using our

proprietary *RARA* or *IRF8* biomarkers. In December 2017, we entered into a clinical supply agreement with Janssen Research and Development, LLC, or Janssen, pursuant to which Janssen agreed to supply us daratumumab for use in the trial. We are no longer enrolling patients in the cohorts of the trial in which SY-1425 was being evaluated as a single agent. We expect to report initial clinical data from the combination cohorts of the trial in the fourth quarter of 2018.

We are continuing to dose patients in the dose-escalation phase of our ongoing Phase 1 clinical trial of SY-1365 and expect to report data from this phase of the trial in the fourth quarter of 2018. Once a maximum tolerated dose is reached in the dose escalation phase of the Phase 1 clinical trial and the recommended dosing schedule is identified, we intend to open expansion cohorts evaluating SY-1365 in multiple ovarian cancer populations as a single agent as well as in combination with carboplatin, a chemotherapeutic agent. The ovarian cancer populations include a 24-patient cohort evaluating SY-1365 as a single agent in patients who have relapsed after three or more prior therapies, a 24-patient cohort evaluating SY-1365 in combination with carboplatin in patients who relapsed after one or more prior therapies but who may still benefit from additional platinum-based treatment, and a 12-patient pilot cohort evaluating SY-1365 as a single agent in primary platinum-refractory disease. We also plan to evaluate SY-1365 in combination with fulvestrant, a hormonal medicine, in 12 patients with hormone-receptor positive, or HR+, HER-2-negative metastatic breast cancer who have progressed after treatment with a CDK4/6 inhibitor plus an aromatase inhibitor. In addition, we plan to evaluate the mechanism of action of SY-1365 in ten patients with any solid tumor accessible for biopsies. We expect that the expansion cohorts in our Phase 1 clinical trial will be open to enrollment in mid-2018.

We currently have five programs in our preclinical and discovery pipeline, including preclinical programs directed to the development of a novel CDK7 inhibitor that can be administered orally, inhibitors of cyclin-dependent kinase 12/13, and inhibitors of an immuno-oncology target, as well as discovery programs related to a gene control target to treat sickle cell disease and in the field of cancer. We plan to nominate a development candidate from one of our preclinical programs during 2018 that we can advance into studies to support a potential investigational new drug application, or IND, filing in 2019. We have and are continuing to 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 a target discovery, research collaboration and option agreement with Incyte Corporation, or Incyte, in January 2018 under which we will use our platform to identify novel therapeutic targets with a focus on myeloproliferative neoplasms. See "— License and Collaboration Agreements – Incyte" below.

Our Focus—Gene Control Medicines

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, including a specific category called enhancers, 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.

While targeted therapies, in which the right drug is matched to the right patient, have dramatically improved the ability to treat certain cancers and other serious diseases, the opportunity to identify new drug targets by sequencing coding regions of DNA is limited, particularly in cancer. Moreover, in cancer, the clinical benefit from inhibiting

abnormal proteins resulting from single genetic alterations is often short-lived due to drug resistance. Furthermore, many serious diseases continue to go unaddressed due to the limitations of current drug discovery approaches. Taken together, these factors underscore the need for fundamentally new approaches to drug discovery and development.

Gene control medicines are intended to modulate the cell's underlying gene expression program, influencing the expression of the crucial set of genes that are associated with disease. The relatively few gene control medicines available today are among the most important targeted therapies and are widely used for their approved indications. Drugs that target transcription factors, such as those which target the estrogen receptor in breast cancer, androgen receptor in prostate cancer and glucocorticoid receptor in inflammation, are important examples of gene control medicines that have produced transformative patient benefits. For example, tamoxifen, a gene control medicine targeting a transcription factor, revolutionized the treatment of certain breast cancers, illustrating the significant therapeutic potential of gene control medicines. However, the difficulty in studying non-coding regions of the genome historically prevented a systematic approach to identifying these critical points of intervention, making gene control a largely untapped field for targeted drug discovery and development.

Based on the work of Syros' scientific founders Richard A. Young, Ph.D., James Bradner, M.D. and Nathanael Gray, Ph.D., and other scientists, there is now a rapidly growing scientific understanding of how alterations in non-coding regions of the genome drive disease and how to modulate gene control targets. One of the seminal discoveries that pushed the field forward came out of Dr. Young's laboratory at the Whitehead Institute for Biomedical Research, or Whitehead. He discovered that a very small unique subset of enhancers, called super-enhancers, are central to orchestrating gene expression programs. These highly specialized regulatory regions of non-coding DNA bring together the cellular components needed for gene expression, assembling large amounts of transcription factors, transcriptional kinases and other transcriptional and regulatory proteins to drive increased expression of genes crucial to a given cell's type and function.

Super-enhancers exist in both normal and diseased cells. In many different diseases, super-enhancers are associated with, and drive the expression of, disease-causing genes. For example, multiple well-known genes that are implicated in cancer, such as *MYC*, are associated with super-enhancers. Notably, analysis of super-enhancers and their associated genes allows us to rapidly and systematically elucidate gene expression programs, pinpointing the genes crucial to the function of a given cell and providing critical insights into changes in gene expression programs that contribute to disease.

These and other discoveries from our scientific founders, coupled with technological advancements, have enabled our pioneering approach to therapeutic gene control. We believe we have built the first proprietary platform designed to systematically and efficiently analyze non-coding regions of the genome in healthy and diseased cells taken from patient tissues to identify alterations in gene expression programs that represent optimal points of therapeutic intervention and develop 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

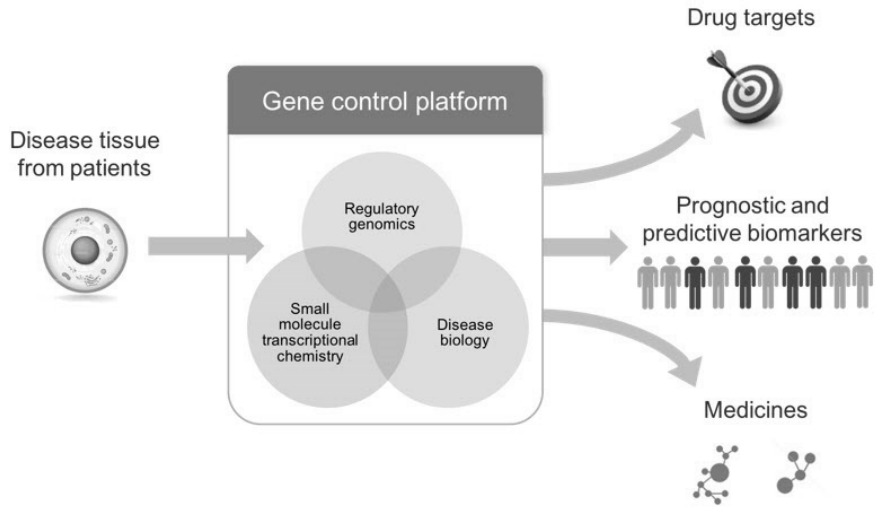
Our proprietary gene control platform consists of two fundamental pillars:

- *Identifying gene control targets that, when modulated with a drug, may provide a therapeutic benefit to a defined patient population.* 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.

- *Drugging gene control targets.* 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; and

- externally focused efforts to link existing drugs to specific patient populations identified through our platform. These externally focused efforts could enable us to identify drugs that we may seek to in-license or acquire or use as starting points for our own drug discovery programs to accelerate our development path, as we did with SY-1425.



Identifying Novel Gene Control Targets

Our long-term goal is to analyze gene expression programs in serious diseases where we believe currently underserved patients can benefit from gene control medicines. We have invested significant resources in building capabilities to discover novel gene control targets and associated biomarkers. Our approach is disease-focused. Our platform consists of technologies and capabilities to analyze gene expression programs directly from patient tissue samples. We do this by employing our expertise and technologies in computational, gene control and cellular biology. We have in-licensed intellectual property from the laboratories of our scientific founders at Whitehead and the Dana-Farber Cancer Institute, Inc., or Dana-Farber. We have significantly improved this licensed technology, including computational algorithms and tissue processing systems, which have produced a highly efficient, scalable approach to analyze gene expression programs using small amounts of patient tissue. These advancements have enabled us to generate a substantial dataset of gene expression programs and to identify targets across many diseases and cell types. Through those efforts, we have identified drug targets in oncology, immuno-oncology, immunology and monogenic diseases, and have validated several of these targets using biological methods to ablate, or knock out, the target gene or chemical methods to modulate the target's activity. The discovery and validation of these targets has led to the identification of our product candidates SY-1425 and SY-1365 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 single gene. Another application of our platform is to characterize the regulatory region associated with such a gene and identify protein or RNA 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.

Validation of Our Approach

We have validated our approach by successfully linking known targets of successful, marketed drugs to super-enhancers in human disease tissue. Additionally, using our platform, we have identified super-enhancers associated with genes linked to the hallmarks of a number of serious diseases.

During 2017, we presented data generated by our scientists in collaboration with researchers at Whitehead in which we analyzed regulatory regions of the genome in cancer stem cell enriched triple-negative breast cancer, or TNBC, cell lines. Cancer stem cells, or CSCs, are known to be involved in resistance to chemotherapies, relapse of disease and development of metastasis. The analysis revealed key genes that may be involved in driving disease relapse and metastasis, with implications for the discovery and development of novel therapies for TNBC. Notably, *TP73*, a gene that encodes a DNA-binding transcription factor called p73, was found to be a core driver of transcriptional circuitry in CSCs, controlling super-enhancer associated genes involved in cell migration, signal transduction and developmental processes. The set of *TP73*-controlled genes provide new leads for drug discovery and development with potential to yield much-needed new therapies for TNBC patients.

We also presented data during 2017 from our collaboration with the University of California, San Diego, in which our platform was used to analyze and compare super-enhancers in cells from pancreatic cancer patient tumors to those in cells from normal pancreatic tissues. These data showed that the leukemia inhibitory factor, or *LIF*, gene demonstrated one of the most significant changes in enhancer size from pancreatic tumors in comparison to normal pancreatic tissue. In preclinical mouse models, *LIF* enhanced the anti-tumor activity of chemotherapy and produced a survival benefit when inhibited using a monoclonal antibody.

Finally, we presented data in the last year showing alterations in regulatory regions of the genome in T cells from patients with systemic lupus erythematosus, or SLE, revealing genes critical for activating T cells and driving disease. Specifically, we found that genes regulated by activation of the *SYK* kinase and *IRF4* transcription factor are significantly enriched in SLE naïve and memory T cells, suggesting that they are key drivers of T cell activation in SLE and a core part of the transcriptional regulatory circuitry driving the disease. These findings provide biological insights into the autoimmune response in lupus that could lead to the identification of novel drug targets and therapeutic approaches to treat SLE.

Drugging Gene Control Targets

We develop product candidates against gene control targets through:

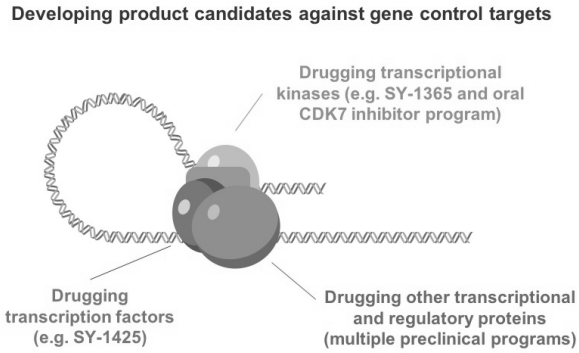
- internal drug discovery efforts focused on creating small molecule drugs targeting transcription factors, transcriptional kinases and other transcriptional and regulatory proteins; and

- linking existing drugs, which we could in-license, to specific patient populations identified through our platform—a strategy we implemented by in-licensing SY-1425 to accelerate our clinical development path.

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 nuclear hormone receptors, transcriptional kinases, chromatin regulators, and other transcriptional and regulatory proteins in order to generate novel chemical matter. 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.

While our platform is designed to identify drug targets across a broad range of therapeutic areas and therapeutic modalities, our drug discovery and development efforts are focused on small molecule drugs to target specialized proteins responsible for gene expression, including transcription factors, transcriptional kinases and other transcriptional and regulatory proteins. Because these specialized proteins play a central role in implementing gene expression

programs, they are among the most promising and high potential gene control targets for therapeutic intervention. The graphic below illustrates our areas of focus for development of product candidates.



Drugging Transcriptional Kinases

SY-1365 demonstrates our ability to identify tumors with transcriptional dependencies and to selectively drug transcriptional kinases. Using our core capabilities in gene control biology and biochemistry, we believe that we have the most advanced inhibitor of CDK7 in clinical development.

Drugging Transcription Factors

Leveraging our expertise in biology, biochemistry and chemistry, we have developed a suite of proprietary screens and assays to demonstrate direct binding of novel transcription factor inhibitors and to directly assess transcription factor inhibition in cells. We are using our capabilities and expertise in structure-based drug design and medicinal chemistry to identify small molecules that that interact with transcription factors.

Linking Existing Drugs to Novel Patient Populations

SY-1425 demonstrates our ability to link existing drugs to novel genomically defined patient populations identified through our platform. We have established a process to systematically screen existing compounds for relationships between drug sensitivity and super-enhancers that we identify in human disease tissue. To date, we have identified multiple drug and enhancer relationships, the most advanced leading to the identification of SY-1425. This program exemplifies the general approach of using our platform to identify compounds that could accelerate our clinical development path.

Our Clinical Programs

SY-1425

Overview

SY-1425 (tamibarotene) is an oral, potent and selective agonist of the transcription factor RARα. In September 2015, we in-licensed from TMRC Co., Ltd., or TMRC, the exclusive right to use intellectual property and data rights controlled by TMRC to develop and commercialize SY-1425 for oncology indications in North America and Europe. We are currently conducting a Phase 2 clinical trial assessing the safety and efficacy of SY-1425 in combination with azacitidine, a hypomethylating agent frequently used to treat patients with AML and MDS, in approximately 25 newly diagnosed AML patients who are not suitable candidates for standard chemotherapy, and in combination with daratumumab, an anti-CD38 therapeutic antibody approved to treat multiple myeloma, in approximately 12 relapsed or refractory AML and higher-risk MDS patients. All patients enrolled or to be enrolled in the trial have been or will be prospectively selected using our proprietary *RARA* or *IRF8* biomarkers. We expect to report initial clinical data from the combination cohorts of the trial in the fourth quarter of 2018.

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 orchestrating gene expression programs and driving increased expression of genes 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 in tumors with the *RARA*-associated super-enhancer, there is an abundance of unliganded RARα, resulting 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.

In collaboration with researchers at Stanford University School of Medicine, we published data in the journal *Cancer Discovery* during 2017 where we used our gene control platform to analyze 66 AML patients' tumor samples and identified six distinct patient subsets based on super-enhancer profiles. The data showed that:

- super-enhancer profiles were strongly associated with survival outcomes, often independent of known genetic mutations in AML;
- the *RARA* super-enhancer was associated with high expression of the *RARA* gene, which codes for the RARα transcription factor;
- *RARA* pathway activation was predictive of response to SY-1425 as demonstrated by reduced proliferation and increased differentiation in AML cells with high *RARA* expression. Moreover, SY-1425 decreased tumor burden and prolonged survival in mouse models in which the mice are implanted with human tumors, which are referred to as patient-derived xenograft models, or PDX models, of AML with high *RARA* expression, while no effect was found on AML cells or PDX models with low *RARA* expression;
- all trans retinoic acid, or ATRA, a less potent and non-selective retinoid, produced no survival benefit in PDX models with high *RARA* expression; and
- SY-1425 induced significant transcriptional changes promoting cell differentiation in AML cells with high *RARA* expression, but little to no transcriptional changes in AML cells with low *RARA* expression.

SY-1425 Development Plan

We plan to develop SY-1425 in North America and Europe for treatment of AML and MDS in genomically defined subsets of patients with either the *RARA* or *IRF8* biomarker, or both. In September 2016, we initiated a multi-center, open-label Phase 2 clinical trial enrolling genomically-defined subsets of patients with AML and MDS pursuant to an IND accepted by the U.S. Food and Drug Administration, or FDA, in May 2016. In the fourth quarter of 2016, an investigational device exemption for the assay being used to select patients with the *RARA* and *IRF8* biomarkers for inclusion in this trial was approved by the FDA. In this trial, we have explored the safety and efficacy of SY-1425 as a single agent, and are continuing to explore the safety and efficacy of SY-1425 in combination with other approved and investigational agents, in the following patient cohorts:

- Single-agent SY-1425 in approximately 25 patients with relapsed or refractory AML or relapsed higher-risk MDS;
- Single-agent SY-1425 in approximately 25 newly-diagnosed AML patients who are not suitable candidates for standard chemotherapy;
- Single-agent SY-1425 in approximately 25 patients with lower-risk, transfusion-dependent MDS;
- SY-1425 in combination with azacitidine in approximately 25 newly-diagnosed AML patients who are not suitable candidates for standard chemotherapy; and

- SY-1425 in combination with daratumumab in approximately 12 patients with relapsed or refractory AML or relapsed higher-risk MDS.

All patients enrolled or to be enrolled in the trial are prospectively selected using our proprietary *RARA* or *IRF8* biomarkers. At the European School of Hematology's 4th International Conference on AML in October 2017, or ESH, we presented data from 201 evaluable patients screened in our ongoing Phase 2 clinical trial demonstrating that approximately 40% of patients were positive for either the *RARA* or *IRF8* biomarker, or both, and that approximately one-third of the relapsed or refractory AML and higher-risk MDS patients tested were biomarker positive.

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. 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 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.

At ASH 2017, we presented clinical data from 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. The median age of patients in the relapsed or refractory and higher-risk AML cohort was 72, with more than half of the patients having poor risk cytogenetics and 45% having two or more prior therapies. The median age of patients in the lower-risk MDS cohort was 76. In 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, with the most commonly-reported adverse events across all grades and causality being elevated triglycerides (36%), fatigue (31%), and dermatologic effects (28%). The most common Grade 3 or 4 adverse event was elevated triglycerides (16%).

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. 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, including:

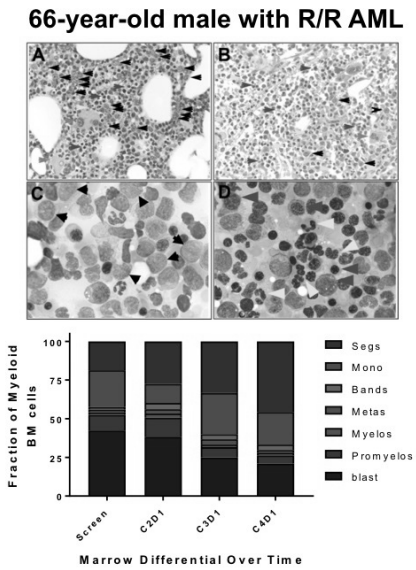
- Nine patients with improvements in hematologic parameters, four of whom achieved hematologic improvement lasting at least eight weeks, as defined by the Revised International Working Group, or IWG, criteria;

- Five patients with reductions in bone marrow blasts, with one relapsed or refractory higher-risk MDS patient achieving a marrow complete response as defined by IWG criteria;

- Thirteen of the 23 (57%) evaluable relapsed or refractory AML and higher-risk MDS patients had stable disease; and

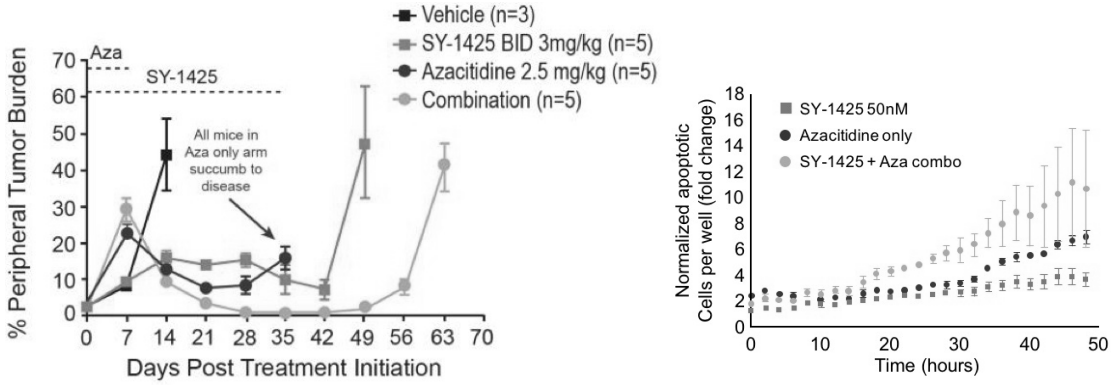
- No patients with lower-risk MDS achieved transfusion independence.

In addition, myeloid differentiation was observed in the bone marrow, consistent with the underlying mechanism of action of SY-1425 as a differentiating agent. The graphic below depicts myeloid differentiation in one relapsed or refractory AML patient starting after one cycle, with marrow blast reduction of greater than 25% beginning after two cycles and continuing to the start of the fourth cycle:



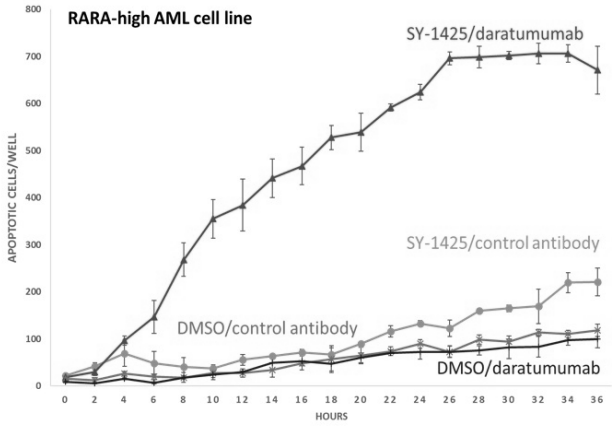
In addition to morphologic evidence of differentiation, immunophenotyping of bone marrow samples demonstrated induction of CD38, a marker of cell differentiation, after one 28-day cycle of treatment in 11 of 13 (85%) patients with pre- and post-treatment immunophenotyping samples.

We are no longer enrolling patients in the cohorts of the trial in which SY-1425 was being evaluated as a single agent. We believe that these clinical data, when combined with preclinical data showing the tumor-killing activity of SY-1425 in combination with azacitidine and with daratumumab, support the ongoing development of SY-1425 as a combination agent. SY-1425 has shown synergistic tumor-killing activity in combination with azacitidine as well as with daratumumab in preclinical models of *RARA* biomarker-positive AML. In combination with azacitidine, SY-1425 demonstrated greater cell death *in vitro* as well as greater clearance of tumor cells in bone marrow and other tissues and greater depth and duration of tumor response in PDX models, compared to either azacitidine or SY-1425 alone:



In combination with daratumumab, SY-1425 induced robust immune cell-mediated tumor death *in vitro*. Notably, AML cells do not normally express high levels of CD38. We have shown that by inducing CD38 expression, SY-1425 sensitizes biomarker-positive AML models to the tumor-killing effects of daratumumab. At the European Hematology Association 22nd Congress held in June 2017, we presented data showing that, by inducing CD38 expression, SY-1425 sensitizes biomarker-positive AML models to the tumor-killing effects of daratumumab. The preclinical studies showed that SY-1425 induced levels of CD38 expression in *RARA*-high AML cells comparable to those in multiple myeloma cells that are known to be responsive to daratumumab, and led to robust cell-mediated tumor

cell death in *RARA*-high AML cells when combined with daratumumab, as shown below:



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 not suitable candidates for standard chemotherapy and in combination with daratumumab in approximately 12 relapsed or refractory AML and higher-risk MDS patients. All patients enrolled or to be enrolled in the trial have been or will be prospectively selected using our proprietary *RARA* or *IRF8* biomarkers. The primary endpoints for each of these cohorts of the trial are overall response rate, as determined by IWG criteria, as well as safety and tolerability. Secondary endpoints include duration of response, hematologic improvement and, for the daratumumab combination cohort, CD38 induction. In December 2017, we entered into a clinical supply agreement with Janssen pursuant to which Janssen agreed to supply us daratumumab for use in the trial. We expect to report initial clinical data from the combination cohorts of the trial in the fourth quarter of 2018.

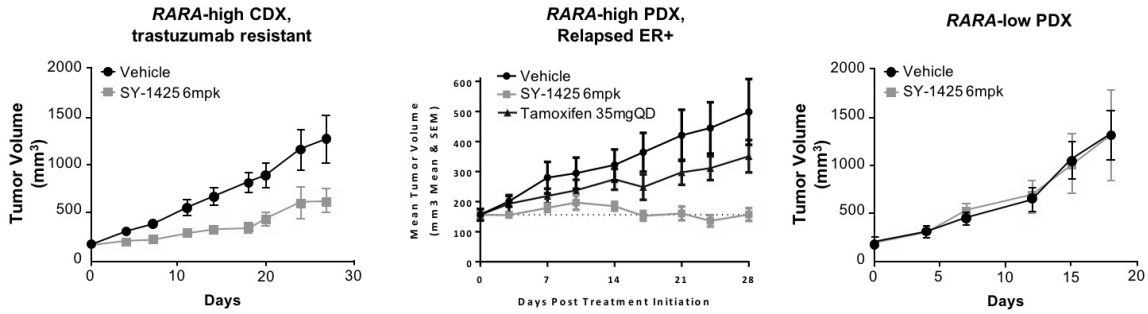
We have entered into an agreement with a third party commercial provider to provide a validated laboratory test under Clinical Laboratory Improvement Amendment, or CLIA, guidelines using a well-established diagnostic platform and approach that is being used to prospectively enroll *RARA* and *IRF8* biomarker-positive 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 these biomarkers, but have not yet selected a platform for development of a companion diagnostic test or entered in to an agreement with a third party for this work. We expect to do so in 2018.

We chose AML and MDS for our initial indications due to high levels of observed efficacy of SY-1425 in our preclinical models, the significant unmet medical need of these patients and the potential for accelerated development. We intend to pursue additional indications, including breast cancer, upon establishing proof-of-concept in AML and MDS. Our preclinical data in breast cancer supports the development of SY-1425 in genomically defined subsets of patients with breast cancers with our *RARA* biomarker. We also believe there are subsets of patients with other tumor types with our *RARA* biomarker and continue to research the role of the super-enhancer associated with *RARA* in additional cancers.

Preclinical Data in Breast Cancer

Additionally, in our preclinical studies in breast cancer, many of which were presented at the San Antonio Breast Cancer Symposium in December 2016, we observed a strong link between sensitivity to treatment with SY-1425 and breast cancer tumors with the *RARA* biomarker. As shown below, SY-1425 was observed to result in significant tumor growth inhibition in PDX models derived from tumors with the *RARA* biomarker but was observed to have no effect in *RARA* biomarker-negative PDX models. Our *in vitro* studies have also shown that SY-1425 increased the anti-

tumor effects of standard-of-care therapies, including tamoxifen and palbociclib, in ER-positive breast cancer cells with high *RARA* expression and lapatinib in HER2-positive breast cancer cells with high RARA expression.



Prior Clinical Data

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 may 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 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 arsenic trioxide 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	Number of 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% vs. 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
RFS = relapse-free survival
BMT = bone marrow transplant

CRm = complete molecular remission
mEFS = median event-free survival
CT = chemotherapy

CRi = complete remission with incomplete blood count recovery
mOS = median overall survival

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.

Tamibarotene was also studied in a Phase 2 clinical trial for the treatment of unselected late-stage non-small cell lung cancer under a previous license between TMRC and a third party. The trial evaluated the efficacy and safety of adding tamibarotene or placebo to paclitaxel and carboplatin in patients with stage IIIb (plus pleural effusion) or IV non-small cell lung cancer. This trial was terminated when interim data suggested that a primary endpoint of progression-free survival for 18 months after starting therapy would not be reached. Interim data also showed that tamibarotene combined with paclitaxel and carboplatin chemotherapy was associated with increased toxicity in this non-selected non-small cell lung cancer patient population.

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. At ESH, we presented data from 201 evaluable patients screened in our ongoing Phase 2 clinical trial demonstrating that approximately 40% of patients were positive for either the *RARA* or *IRF8* biomarker, or both, and that approximately one-third of the relapsed or refractory AML and higher-risk MDS patients tested were biomarker positive.

There are an estimated 33,000 new AML diagnoses in the United States, Canada and the five largest European countries each year. While several new drugs for the treatment of AML have been approved in the last year, AML remains an area of significant unmet medical need. According to the American Cancer Society, newly diagnosed AML patients in the United States have a 27% five-year survival rate. More than half of newly diagnosed AML patients are elderly or unfit for treatment with standard therapies, leaving this group with limited treatment options and an average survival of less than one year. 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 10,000 cases of relapsed or refractory AML each year in the United States, Canada and the five largest European countries each year. 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 are approximately 32,000 new MDS diagnoses in the countries listed above each year, with up to one-third of these newly diagnosed patients estimated to be likely to progress to AML. Of these patients, approximately 7,500 MDS patients have newly-diagnosed, higher-risk MDS. In the United States, newly-diagnosed, higher-risk MDS patients are expected to survive for 0.8-1.6 years, and relapsed or refractory higher-risk AML patients have an average survival of less than six months. As with AML, treatment options for these patients are limited, with no new drugs having been approved for the treatment relapsed or refractory, higher-risk MDS in over a decade.

There are an estimated 2,500 new APL cases diagnosed in the United States, Canada and the five largest European countries each year. Despite advances in treating APL, approximately 20-30% of APL patients relapse and require salvage therapy.

SY-1365

Overview

SY-1365 is a highly potent and selective small molecule CDK7 inhibitor. CDK7, a member of the cyclin-dependent kinase, or CDK, family, is a transcriptional kinase that plays a central role in the expression of key tumor-driving genes, transcription factors, and anti-apoptotic proteins. CDK7 activity has been implicated in various solid tumors with transcriptional dependencies. Inhibiting CDK7 preferentially lowers the expression of disease-driving transcription factors controlled by super-enhancers, and results in the preferential killing of cancer cells over non-cancerous cells. Using our platform, we have generated several potent and selective small molecule CDK7 inhibitors, including SY-1365.

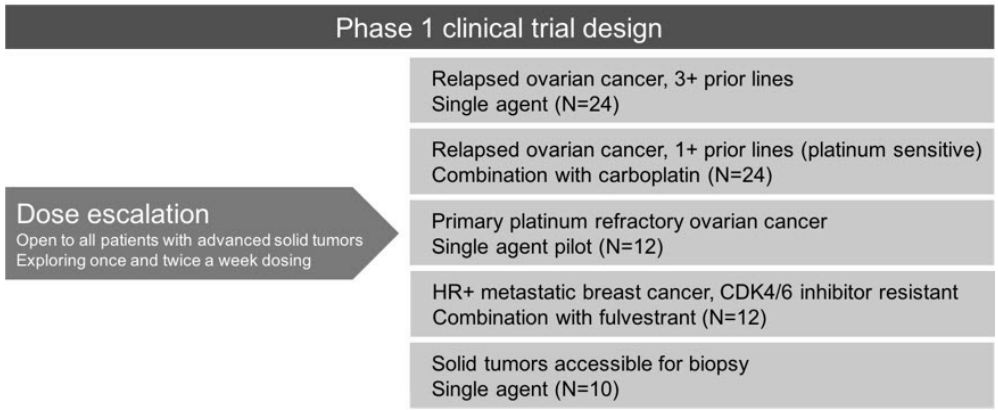
SY-1365 is currently in a Phase 1 clinical trial in patients with advanced solid tumors. We believe that SY-1365 is the most advanced selective CDK7 inhibitor in clinical development. SY-1365, alone and in combination with other therapeutic agents, has shown significant anti-proliferative and pro-apoptotic activity in multiple *in vitro* and *in vivo* models of difficult-to-treat solid tumors, including ovarian and breast cancers. SY-1365 has induced anti-tumor activity in both cell line-derived xenograft and patient-derived xenograft models, including tumor regressions at a twice weekly dosing regimen consistent with the initial regimen being evaluated in our Phase 1 clinical trial. SY-1365 has also shown to anti-tumor activity in models of blood cancers such as acute leukemias, as evidenced by *in vitro* cell death or complete tumor growth inhibition in cell-derived xenografts. Finally, SY-1365 has been shown to lower the expression of oncogenic transcription factors, including *MYC*, a mechanistic effect consistent with inhibition of CDK7.

SY-1365 Clinical Development Plan

In April 2017, the FDA accepted our investigational new drug, or IND, application to advance SY-1365 into a Phase 1 clinical trial in patients with advanced solid tumor malignancies for whom standard curative or palliative measures do not exist or are no longer effective. This trial began enrolling patients in the second quarter of 2017. The trial is testing 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 include assessing pharmacodynamic changes and early signs of biological activity using biomarkers and clinical efficacy as measured by response rate using radiographic measures. We are currently exploring both a twice-weekly and a once-weekly dosing regimen, and we anticipate that approximately 35 patients will be enrolled in the dose escalation phase of the trial.

Once a maximum tolerated dose is reached in the dose escalation phase of the Phase 1 clinical trial and the recommended dosing schedule is identified, we intend to open expansion cohorts evaluating SY-1365 in multiple ovarian cancer populations as a single agent as well as in combination with carboplatin, a chemotherapeutic agent. The ovarian cancer populations include a 24-patient cohort evaluating SY-1365 as a single agent in patients who have relapsed after three or more prior therapies, a 24-patient cohort evaluating SY-1365 in combination with carboplatin in patients who relapsed after one or more prior therapies but who may still benefit from additional platinum-based treatment, and a 12-patient pilot cohort evaluating SY-1365 as a single agent in primary platinum-refractory disease. We also plan to evaluate SY-1365 in combination with fulvestrant, a hormonal medicine, in 12 patients with HR+, HER-2-negative metastatic breast cancer who have progressed after treatment with a CDK4/6 inhibitor and aromatase inhibitor.

In addition, we plan to evaluate the mechanism of action of SY-1365 in ten patients with any solid tumor accessible for biopsies. A schematic of our Phase 1 clinical trial of SY-1365 is below:

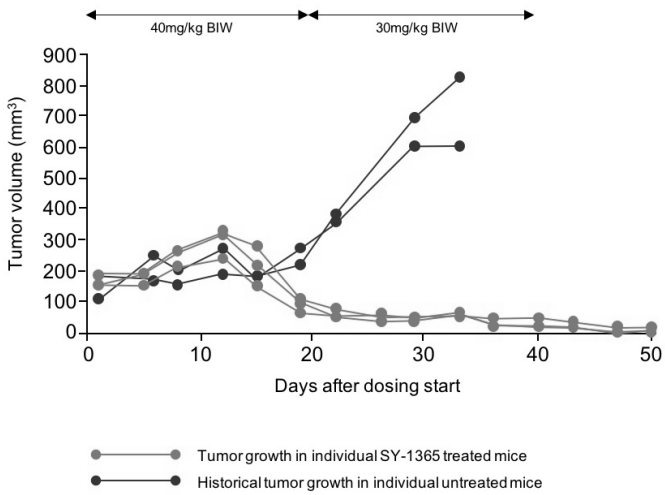


We expect that the expansion cohorts in our Phase 1 clinical trial will be open to enrollment in mid-2018 and that we will report clinical data from the dose-escalation phase of our Phase 1 trial, including safety and pharmacokinetic/pharmacodynamic data, in the fourth quarter of 2018.

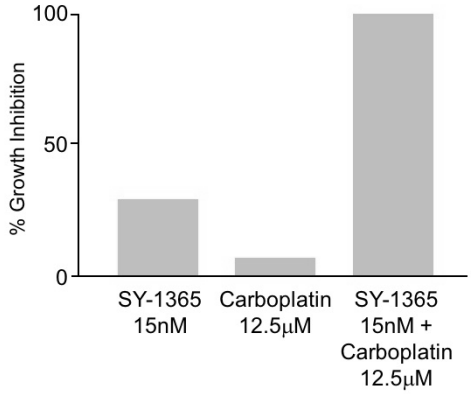
Our Preclinical Data

Our clinical development program for SY-1365 is based on a robust preclinical development program showing significant anti-proliferative activity of SY-1365 in multiple *in vitro* and *in vivo* models of difficult-to-treat solid tumors and blood cancers, including ovarian cancer, breast cancer and AML.

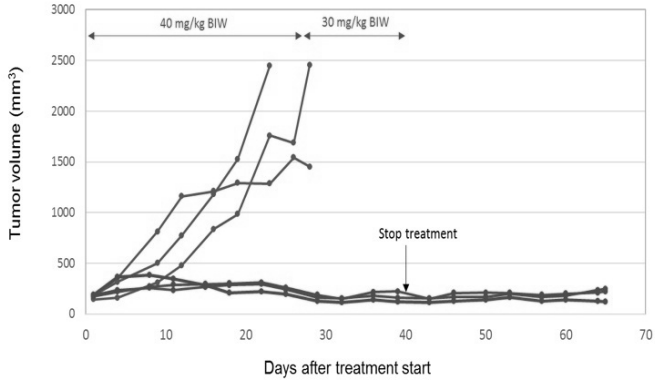
To evaluate the *in vivo* activity of SY-1365 in ovarian cancer, we evaluated SY-1365 in a number of patient-derived xenograft models derived from heavily-pretreated ovarian cancer patients and compared tumor growth in mice administered SY-1365 twice-weekly at the maximum tolerated dose in that species to untreated mice. Significant tumor growth inhibition was observed in many of these models following administration of SY-1365, with data from a representative model set forth in the graphic below:



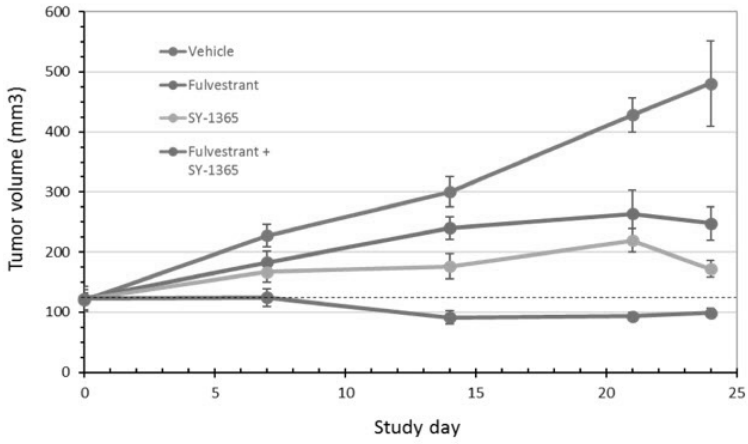
We have also shown the synergistic effect of treatment with SY-1365 and platinum-based chemotherapy in several ovarian cancer cell lines, as exemplified in the graphic below:



The inhibitory activity of SY-1365 was evaluated *in vitro* in many breast cancer cell lines, representing different subgroups of breast cancer. SY-1365 showed anti-tumor activity in all subgroups, inducing cell death in 15 of 19 TNBC cell lines and 17 of 21 HR+ and HER2-positive cell lines. At the San Antonio Breast Cancer Conference held in December 2017, we presented the results of our analysis of the anti-tumor activity of SY-1365 in xenograft models of TNBC. In the graphic below, we showed a complete response in mice administered SY-1365 twice weekly at the maximum tolerated dose in that species as compared to untreated mice.



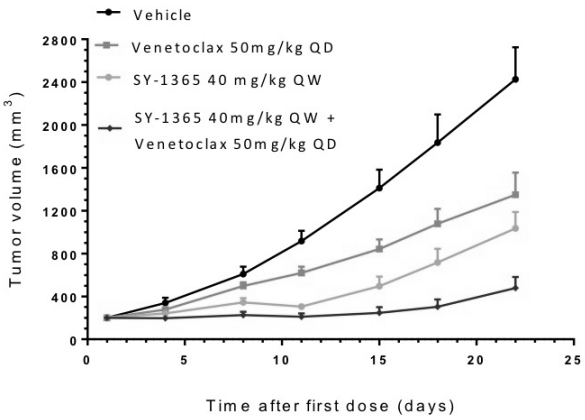
We, together with several of our academic collaborators, have demonstrated that SY-1365 could inhibit many HR+ cancer cells, including those with a form of acquired resistance to a class of hormonal treatments known as aromatase inhibitors, and that SY-1365 was able to inhibit breast cancer cell lines *in vitro* that no longer respond to inhibitors of CDK4/6. In addition, SY-1365 showed *in vitro* synergy with fulvestrant in several HR+ breast cancer cell lines. SY-1365 also showed a combination effect with fulvestrant in an *in vivo* model of HR+ breast cancer, as shown in the graphic below. We believe that these data, taken together, provide a mechanistic rationale for evaluating SY-1365 in combination with fulvestrant in patients with HR+ metastatic breast cancer who have progressed following treatment with a CDK4/6 inhibitor plus an aromatase inhibitor.



We also believe that SY-1365 has potential in blood cancers as well as in other solid tumor malignancies. The preclinical rationale for potential development of SY-1365 in blood cancers includes data we presented at ASH 2017 demonstrating that SY-1365:

- inhibited proliferation *in vitro* in leukemia and lymphoma cells, as well as leukemia cells from primary patient cultures;
- induced cell death in the majority of AML, leukemia and lymphoma cell lines tested; and
- inhibited tumor growth, including inducing tumor regression, using bi-weekly dosing in preclinical mouse models of AML.

In addition, we demonstrated that SY-1365 synergized with venetoclax, an investigational product being developed in AML, in AML cell lines *in vitro*, and that, as shown in the graphic below, the administration of SY-1365 plus venetoclax in an *in vivo* model resulted in greater tumor growth inhibition than either agent alone.



We also presented data at the 2017 AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics conference showing the relationship between the pharmacokinetic, pharmacodynamic and anti-tumor activity of SY-1365 in multiple preclinical models of TNBC and AML, across a range of doses and regimens from daily to weekly dosing. These data showed a prolonged pharmacodynamic effect, as measured by CDK7 target occupancy, with a half-life of approximately three days, which supports the intermittent dosing regimen being evaluated in our ongoing Phase 1 clinical trial. We are using an assay measuring target occupancy as a target engagement marker in this trial. These data also showed a dose-dependent relationship between CDK7 target occupancy and anti-tumor activity in a preclinical model of AML, and sustained tumor regressions in multiple *in vivo* models using a twice-weekly dosing regimen.

SY-1365 Market Opportunity

With SY-1365, we believe 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-1365 is expected to be in ovarian cancer and HR+ breast cancer.

Ovarian cancer is the fifth most common cause of cancer death in women. There are an estimated 59,000 ovarian cancer diagnoses each year in what we refer to as the developed pharmaceutical markets – the United States, Canada, Japan and the five largest European countries by population, which are Germany, the United Kingdom, France Spain and Italy. Of these, approximately 70% have high-grade serous ovarian cancer and present with advanced disease at initial diagnosis. The standard of care treatment for these patients is platinum-based chemotherapy. It is estimated that 10-15% of these patients are "platinum-refractory," which means that they progress during, or in less than one month of completion of, platinum-based treatment. There are limited treatment options for platinum-refractory patients. Approximately 30% of these patients are "platinum-resistant," which means that they progress within six months of completing platinum-based treatment. We believe that subsequent treatment options for these patients at the present time have limited activity and significant toxicities. Approximately 55-60% of these patients are "platinum-sensitive," which means that they initially respond to platinum-based treatment, but progress after six months or more. The majority of these patients relapse within three to five years. The planned expansion cohorts of our Phase 1 clinical trial of SY-1365 include patients who have progressed after platinum-based treatments.

Breast cancer is the most common tumor type in women and is the leading cause of cancer death in women worldwide. According to the American Cancer Society, approximately 266,000 new breast cancer cases will be diagnosed in the United States in 2018, with approximately 41,000 deaths from the disease. Approximately 80% of breast cancers express estrogen receptors, progesterone receptors, or both. Hormone-based therapies are the cornerstone for these HR+ cancers. In metastatic breast cancer, AIs are frequently used as a first-line treatment option. Recent approvals of a class of drugs that inhibit CDK4/6, such as palbociclib and ribociclib, have resulted in their use in combination with AIs for the treatment of HR+, HER2-negative, breast cancers. Patients who relapse following treatment with an AI in combination with a CDK4/6 inhibitor currently have few effective treatment options.

Other Programs

We currently have five programs in our preclinical and discovery pipeline, including preclinical programs directed to the development of a CDK7 inhibitor that can be administered orally, inhibitors of cyclin-dependent kinase 12/13, and inhibitors of an immuno-oncology target, as well as discovery programs related to a gene control target to treat sickle cell disease and in the field of cancer. We plan to nominate a development candidate from one of our preclinical programs during 2018 that we can advance into studies to support a potential IND filing in 2019, consistent with our objective of filing, on average, an IND every other year.

We are 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 will use our platform to identify novel therapeutic targets with a focus on myeloproliferative neoplasms. See "—License and Collaboration Agreements–Incyte" below.

Research and Development Expense

During the years ended December 31, 2017, 2016 and 2015, our research and development expenses were $41.9 million, $37.8 million and $24.4 million, respectively. For additional information regarding our research and development expense as well as our revenues, operating loss, and total assets, see the sections of this report entitled, "Financial Statements" in Part II, Item 8 and "Management's Discussion and Analysis of Financial Condition and Results of Operations" in Part II, Item 7.

Intellectual Property

We file patent applications directed to our gene control platform, proprietary composition of matter and product candidates in an effort to establish intellectual property positions regarding all aspects of our business, including new chemical entities, or NCEs, and uses of these NCEs in the treatment of diseases. As of February 28, 2018, we own two issued U.S. patents, 12 pending U.S. provisional patent applications, twelve U.S. pending patent applications, 41 foreign applications pending in a number of jurisdictions, including Europe, Australia, Japan, China, and Canada, and four pending Patent Cooperation Treaty, or PCT, patent applications. In addition, as of February 28, 2018, we have exclusively licensed six issued U.S. patents, three U.S. pending patent applications, five issued foreign patents and 12 foreign patent applications pending in a number of jurisdictions, including Australia, Canada, China, Europe, and Japan. A significant portion of our owned and licensed pending patent applications pertain to our product candidates and associated biomarkers, key discovery and preclinical programs, specifically our CDK7 inhibitor program, and transcription factor modulators, and our gene control platform.

Our intellectual property portfolio as of February 28, 2018 is summarized below. For some of our pending patent applications, prosecution has yet to commence. Prosecution is a lengthy process, during which the scope of the claims initially submitted for examination by the U.S. Patent and Trademark Office, or USPTO, is often significantly narrowed by the time they issue, if they issue at all. We expect this to be the case with respect to our pending patent applications referred to below. In addition, we may elect to abandon prosecution of some of our pending patent applications, particularly outside of the United States, if we determine that these applications do not have strategic significance to our programs or platform.

SY-1425

Our owned intellectual property portfolio for SY-1425 contains two issued U.S. patents, two U.S. pending patent applications, 11 foreign applications pending in a number of jurisdictions, including Europe, Australia, Japan, China, and Canada, and three pending PCT patent applications directed to patient stratification methods based on biomarkers, combinations and methods of use for agonists of RARα, including SY-1425. One of our issued patents, U.S. Patent 9,845,508, covers a method of diagnosing and treating AML patients by determining whether they have elevated levels of RARA messenger RNA, or mRNA, and, if they do, administering SY-1425. The second patent, U.S. Patent 9,868,994, covers a method of treating AML and MDS by administering SY-1425 to patients known to have elevated levels of IRF8 mRNA. For purposes of these patents, AML does not include acute promyelocytic leukemia, or APL. We believe that our currently-issued U.S. patents related to our SY-1425 program are eligible for listing in the U.S. Food and Drug Administration's Orange Book. The U.S. patents and pending applications and any U.S. or non-U.S. applications claiming priority to these pending applications, if issued, have statutory expiration dates no earlier than March 2036.

In addition, we are exclusively licensed in North America and Europe under two issued U.S. patents, and five issued foreign patent applications in Canada and Europe, directed to pharmaceutical kits and drug combinations comprising tamibarotene and certain other chemotherapeutic agents, certain formulations of tamibarotene, and crystal forms of tamibarotene and their preparation. One licensed issued U.S. patent covering formulations has a statutory expiration date of April 2028. The other licensed issued U.S. patent covering crystals has a statutory expiration date of August 2021. Patent term adjustments or patent term extensions could result in later expiration dates for each of these patents. We do not have composition of matter patent protection with respect to SY-1425.

SY-1365

The intellectual property portfolio for SY-1365 and our other CDK7 inhibitors contains patent applications directed to compositions of matter for our compounds and analogs, compositions of matter for CDK7 inhibitors having different structural features (*i.e.,* different compound families), as well as methods of use, biomarkers, and formulations for these novel compounds. As of February 28, 2018, we own six pending U.S. patent applications, 29 pending foreign applications in a number of jurisdictions, including Europe, Canada, China, Japan and Australia and one pending PCT patent application and seven pending U.S. provisional applications, directed to this program. Any U.S. or non-U.S. patents issuing from these pending applications or applications claiming priority to the pending applications covering our compounds and related methods of use will have a statutory expiration date ranging from October 2034 to January 2039. Patent term adjustments or patent term extensions could result in later expiration dates.

We are also exclusively licensed under one U.S. patent, two pending U.S. patent applications and 11 pending foreign patent applications in a number of jurisdictions, including Australia, Canada, Europe, and Japan, directed to this program.

Other Programs

The intellectual property portfolio for our other programs 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 February 28, 2018, we own five U.S. provisional patent applications and three U.S. patent applications and are exclusively licensed to two issued U.S. patents directed to our other programs. The licensed U.S. patents have statutory expiration dates of July 2032 and November 2033. 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 intellectual property 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 February 28, 2018, 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 one issued U.S. patent, one U.S. pending patent application and one pending foreign patent application in Europe, 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. patent has 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.

The term of individual patents depends upon the legal term for patents in the countries in which they are obtained. In most countries, including the United States, the patent term is 20 years from the earliest filing date of a non-provisional patent application. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the USPTO in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier filed patent. The term of a patent that covers a drug or biological product may also be eligible for patent term extension when FDA approval is granted, provided statutory and regulatory requirements are met. See "—Government Regulation and Product Approvals—Marketing Authorization and Exclusivity" below for additional information on such exclusivity. In the future, if and when our product candidates receive approval by the FDA or foreign regulatory authorities, we expect to apply for patent term extensions on issued patents covering those drugs, depending upon the length of the clinical trials for each drug and other factors. There can be no assurance that any of our pending patent applications will issue or that we will benefit from any patent term extension or favorable adjustment to the term of any of our patents.

As with other biotechnology and pharmaceutical companies, our ability to maintain and solidify our proprietary and intellectual property position for our product candidates and technologies will depend on our success in obtaining effective patent claims and enforcing those claims, if granted. Our pending patent applications, and any patent applications that we may in the future file or license from third parties may not, however, result in the issuance of patents. We also cannot predict the breadth of claims that may be allowed or enforced in our patents. Any issued patents that we may receive in the future may be challenged, invalidated or circumvented. For example, we cannot be certain of the priority of inventions covered by pending third-party patent applications. If third parties prepare and file patent applications in the United States that also claim technology or therapeutics to which we have rights, we may have to participate in interference proceedings in the USPTO to determine priority of invention, which could result in substantial costs to us, even if the eventual outcome is favorable to us, 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, we rely upon unpatented trade secrets and know-how and continuing technological innovation to develop and maintain our competitive position. We seek to protect our proprietary information, in part, by executing confidentiality agreements with our collaborators and scientific advisors, and non-competition, non-solicitation, confidentiality, and invention assignment agreements with our employees and consultants. We have also executed agreements requiring assignment of inventions with selected scientific advisors and collaborators. 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 global target discovery collaboration with Incyte under which we intend to identify and validate novel therapeutic targets with a focus on myeloproliferative neoplasms. By entering into this collaboration, we aim to use our platform to benefit patients with diseases beyond our current areas of focus, although we do not have any rights to commercialize any products arising from this collaboration. These collaborations impose certain performance obligations on us. We may enter into agreements similar to this one in the future.

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.

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 will receive 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. Incyte will have exclusive worldwide rights to develop and commercialize any therapies under the collaboration that modulate those validated targets.

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. Our activities under this agreement are subject to a joint research plan and, subject to certain exceptions, Incyte will be responsible for funding our activities under the research plan, including amounts in excess of the pre-paid research funding amount. 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 option 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. 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.

We are obligated to make a payment to Whitehead representing a percentage of the up-front cash consideration and equity premium received from Incyte.

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.

Dana-Farber Cancer Institute, Inc.

In February 2013, we entered into a license agreement with Dana-Farber pursuant to which we were granted an exclusive worldwide, sublicensable license under specified patents relating to CDK7 inhibitors and *JNK* inhibitors owned or controlled by Dana-Farber. The license is for all fields of use and subject to certain rights retained by Dana-Farber for internal non-commercial research, academic/teaching and government purposes. Subject to certain restrictions, Dana-Farber granted us an option to obtain an exclusive commercial license to certain improvements created by Dana-Farber during the first three years of the agreement, which would be negotiated in good faith and incorporated into this agreement. In connection with the agreement, we paid Dana-Farber an upfront licensing fee and a milestone payment based on our first round of funding, such payments totaling $175,000, in addition to past patent expenses. We are obligated to pay Dana-Farber annual license maintenance fees that are creditable against other payments and royalties due under the agreement and to make milestone payments of up to an aggregate of $3.4 million for each of the first two licensed products in connection with the achievement of certain clinical and regulatory milestones. In addition, we are required to pay Dana-Farber a tiered royalty on net sale of licensed products by us, our affiliates and sublicensees ranging from low single digit to mid-single digit percentages, subject to certain adjustments, as well as a tiered mid-single digit to low double-digit percentage of sublicense income. Our royalty and sublicensing income payment obligations are further subject to apportionment between designated agreements existing among us, Dana-Farber and

Whitehead. We are required to meet certain diligence milestones and to use commercially reasonable efforts to, among other things, develop and commercialize one or more licensed products or processes and to make one or more licensed products or processes reasonably available to the public. The agreement contains specified diligence activities that if met on an annual basis would be deemed to satisfy some of our diligence obligations for the particular year. The agreement, unless earlier terminated by us or Dana-Farber, will remain in effect until the expiration or abandonment of the licensed patent rights. We have the right to terminate the agreement for any reason provided that we provide Dana-Farber the required notice and we pay all undisputed amounts due to Dana-Farber at the time of termination. Dana-Farber has the right to terminate the agreement if we cease doing business, or if we do not pay them the amounts owed under the agreement and fail to cure, or if we commit and fail to cure a material breach under the agreement, or if our successor does not agree in writing to be bound by this agreement within the designated period following assignment.

Whitehead Institute for Biomedical Research and Dana-Farber Cancer Institute, Inc.

In April 2013, we entered into a license agreement with Whitehead and Dana-Farber, pursuant to which we were granted an exclusive, sublicensable with certain restrictions, license under specified patents relating to *MYC* modulators owned or controlled by Whitehead and Dana-Farber, to make, have made, use, sell, offer for sale and import products and to perform and have performed licensed processes, in each case, in the applicable field. We were granted a non-exclusive license to certain materials for the practice of our exclusive licenses. The licenses are subject to certain rights retained by Dana-Farber and Whitehead for internal non-commercial research, academic/teaching and government purposes. Commencing five years after the effective date and subject to certain terms and conditions, the agreement requires us to negotiate and potentially issue mandatory sublicenses under the patent rights outside of human health and therapeutics for fields and products that are not directly competitive with products in active development or commercialization by us, our affiliates or sublicensees.

In connection with the agreement, we paid Whitehead an upfront licensing fee, and a milestone payment based on our first round of funding, such payments totaling $100,000, in addition to past patent expenses. We are obligated to pay Whitehead annual license maintenance fees that are creditable against other payments and royalties due under the agreement and to make milestone payments of up to an aggregate of $3.4 million in connection with the achievement of certain clinical and regulatory milestones. In addition, we are required to pay Whitehead a royalty on net sales of the various products by us, our affiliates and sublicensees ranging from low single digit to mid-single digit percentages, subject to certain adjustments, including a lower royalty on products identified through the use of certain licensed products or processes. In addition, we are required to pay a tiered mid-single digit to low double-digit percentage of our and our affiliates' sublicense income and income we receive from the performance of licensed processes. Our royalty, sublicensing and licensed process income payment obligations are further subject to apportionment between designated agreements existing among us, Dana-Farber and Whitehead. In connection with the agreement, we also issued an aggregate of 98,099 shares of our common stock to Whitehead. We are required to achieve certain diligence milestones within the specified timeframes, and failure to do so may result in our license under certain patent rights being converted to non-exclusive or otherwise be deemed a material breach of the agreement. The agreement further requires that we use commercially reasonable efforts to, among other things, develop and commercialize one or more licensed products or processes and to make one or more licensed products or processes reasonably available to the public. The agreement contains specified diligence activities that if met on an annual basis would be deemed to satisfy some of our diligence obligations for the particular year. The agreement, unless earlier terminated by us, Whitehead or Dana-Farber, will remain in effect until the expiration or abandonment of the licensed patent rights. We have the right to terminate the agreement for any reason, provided that we provide Dana-Farber and Whitehead the required notice and we pay all undisputed amounts due to Whitehead and Dana-Farber at the time of termination. Whitehead and Dana-Farber have the right to terminate the agreement if we cease doing business, or if we do not pay them the amounts owed under the agreement and fail to cure, or if we commit and fail to cure a material breach under the agreement, or if our successor does not agree in writing to be bound by this agreement within the designated period following assignment.

Whitehead Institute for Biomedical Research

In April 2013, we entered into a license agreement with Whitehead, which we refer to as the Whitehead license agreement, pursuant to which we were granted a worldwide license under specified patents relating to super-enhancers owned or controlled by Whitehead. This license was exclusive in all fields until April 2016, and can remain exclusive thereafter, on a field-by-field basis, as long as we can demonstrate that we are using commercially reasonable efforts in the applicable field, and if we are not using such commercially reasonable efforts in such applicable field, our license rights would become non-exclusive with respect to such field. As of February 28, 2018, our license continued to be

exclusive in all fields. We were also granted a non-exclusive license to use certain Whitehead materials in connection with the practice of the licensed Whitehead patents. In connection with the Whitehead license agreement, we paid Whitehead an upfront licensing fee of $30,000. In connection with the agreement, we also issued an aggregate of 73,575 shares of our common stock to Whitehead. We are obligated to pay Whitehead annual license maintenance fees that are creditable against other payments and royalties due under the agreement. In addition, we are required to pay Whitehead a tiered royalty on our net sales ranging from low single digit to mid-single digit percentages, a lower royalty on products identified through the use of licensed products or processes, and a tiered mid-single digit to low double digit percentage of sublicense income, which steps down depending on time, development stage of the products or processes and payments made to Whitehead, and patent expenses of Whitehead in connection with the licensed patents. We are required to use commercially reasonable efforts to, among other things, develop and commercialize one or more licensed products or processes and to make one or more licensed products or products reasonably available to the public. The Whitehead license agreement, unless earlier terminated by us or Whitehead, will remain in effect until the expiration or abandonment of the licensed patent rights. We have the right to terminate the Whitehead license agreement for any reason upon three months' notice to Whitehead, provided that we pay all undisputed amounts due to Whitehead at the time of termination. Whitehead has the right to terminate the Whitehead license agreement immediately if we cease doing business, or if we do not pay Whitehead the amounts owed under the agreement or commit a material breach under the agreement, Whitehead has the right to terminate after we have had an opportunity to cure the breach.

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 or MDS. We will select patients for our clinical trials based on high-levels of RARα as measured by our proprietary *RARA* and *IRF8* biomarkers. We are aware of four new drugs approved by the FDA during 2017 for the treatment of AML or patient subsets within AML: midostaurin, enasidanib, daunorubicin + cytarabine liposome, and gemtuzumab. SY-1425 may also face competition from other investigational products currently in clinical development for AML and MDS, including venetoclax, which is currently being evaluated by AbbVie, Inc. in two randomized pivotal studies in patients with AML, as well as investigational products in development from Takeda Pharmaceutical Co. Ltd., Daiichi Sankyo Company, Limited, Agios Pharmaceuticals, Inc., Novartis AG, Bristol-Myers Squibb Co., Eli Lilly & Co., Eisai Inc., Celgene Corporation, Pfizer, Inc., Incyte Corporation and FORMA Therapeutics, LLC. We are aware of only one other selective RARα program, a compound in development from Io Therapeutics, Inc. which, according to a government-sponsored website, is in an investigator initiated Phase 1/2 study in a non-selective patient group in relapsed and refractory AML, high-risk MDS and chronic myelomonocytic leukemia.

SY-1365

We are conducting a Phase 1 clinical trial of SY-1365 in patients with advanced solid tumors and plan to open expansion cohorts in various ovarian and breast cancer populations once we establish the maximum tolerated dose during the dose escalation phase of the trial. We believe that SY-1365 is the most advanced selective CDK7 inhibitor in clinical development. We are aware of an oral CDK7 inhibitor being developed by Carrick Therapeutics Ltd. that has recently entered Phase 1 clinical development, and are aware of several other selective CDK7 inhibitor programs that we believe are in preclinical development, including programs from Aurigene Discovery Technologies Ltd., Ube Industries Ltd., Qurient Co. Ltd., and Beta Pharma, Inc. SY-1365 may face competition from these selective 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, including the EU, extensively regulate, among other things, the research, development, testing, manufacture, pricing, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of biopharmaceutical products. The processes for obtaining marketing approvals in the United States and in foreign countries and jurisdictions, along with compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

Approval and Regulation of Drugs in the United States

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

An applicant seeking approval to market and distribute a new drug in the United States generally must satisfactorily complete each of the following steps before the product candidate will be licensed 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 applicable 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, on April 28, 2008, the FDA amended its regulations governing the acceptance of foreign clinical studies not conducted under an investigational new drug application as support for an IND or a new drug application. The final rule provides that such studies must be conducted in accordance with 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.

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 2018 is $2,421,495 for an application requiring clinical data. The sponsor of an approved NDA is also subject to an annual program fee, which for fiscal year 2018 is $304,162. 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 the safe use of the product. 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 FDASIA. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

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

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

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 new drug products are based on well controlled studies that provide 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 product has been approved, as well as for any new indication sought by the Section 505(b)(2) applicant.

Abbreviated New Drug Applications for Generic Drugs

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

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

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

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

The FDA must establish a priority review track for certain generic drugs, requiring the FDA to review a drug application within eight 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.

The 21st Century Cures Act

On December 13, 2016, President Obama signed the 21st Century Cures Act, or Cures Act, into law. The Cures Act is designed to modernize and personalize healthcare, spur innovation and research, and streamline the discovery and development of new therapies through increased federal funding of particular programs. It authorizes increased funding for the FDA to spend on innovation projects. The new law also amends the Public Health Service Act, or PHSA, to reauthorize and expand funding for the NIH. The Cures Act establishes the NIH Innovation Fund to pay for the cost of development and implementation of a strategic plan, early stage investigators and research. It also charges NIH with leading and coordinating expanded pediatric research. Further, the Cures Act directs the Centers for Disease Control and Prevention to expand surveillance of neurological diseases.

With amendments to the FDCA and the PHSA, Title III of the Cures Act seeks to accelerate the discovery, development, and delivery of new medicines and medical technologies. To that end, and among other provisions, the Cures Act reauthorizes the existing priority review voucher program for certain drugs intended to treat rare pediatric diseases until 2020; creates a new priority review voucher program for drug applications determined to be material national security threat medical countermeasure applications; revises the FDCA to streamline review of combination product applications; requires FDA to evaluate the potential use of "real world evidence" to help support approval of new indications for approved drugs; provides a new "limited population" approval pathway for antibiotic and antifungal drugs intended to treat serious or life-threatening infections; and authorizes the FDA to designate a drug as a "regenerative advanced therapy," thereby making it eligible for certain expedited review and approval designations.

FDA Approval and Regulation of Companion Diagnostics

If safe and effective use of a therapeutic depends on an *in vitro* diagnostic, then the FDA generally will require approval or clearance of that diagnostic, known as a companion diagnostic, at the same time that the FDA approves the therapeutic product. In August 2014, the FDA issued final guidance clarifying the requirements that will apply to approval of therapeutic products and *in vitro* companion diagnostics. According to the guidance, 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.

Health care Law and Regulation

Health care providers and third-party payors play a primary role in the recommendation and prescription of drug products that are granted marketing approval. Arrangements with providers, consultants, third-party payors and customers are subject to broadly applicable fraud and abuse, anti-kickback, false claims laws, patient privacy laws and regulations and other health care laws and regulations that may constrain business and/or financial arrangements. Restrictions under applicable federal and state health care laws and regulations, include the following:

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

- the federal civil and criminal false claims laws, including the civil False Claims Act, and civil monetary penalties laws, which prohibit individuals or entities from, among other things, knowingly presenting, or

causing to be presented, to the federal government, claims for payment that are false, fictitious or fraudulent or knowingly making, using or causing to made or used a false record or statement to avoid, decrease or conceal an obligation to pay money to the federal government.

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

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

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

- the 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.

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. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Pharmaceutical Insurance Coverage and Health Care Reform

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

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

product does not imply that an adequate reimbursement rate will be approved. Further, one payor's determination to provide coverage for a product does not assure that other payors will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payor to payor.

The containment of health care costs also has become a priority of federal, state and foreign governments and the prices of products have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with 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 since the ACA was enacted. These changes include the Budget Control Act of 2011, which, among other things, led to aggregate reductions to Medicare payments to providers of up to 2% per fiscal year that started in 2013 and will stay in effect through 2024 unless additional Congressional action is taken, and the American Taxpayer Relief Act of 2012, which, among other things, reduced Medicare payments to several types of providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Further, there have been several recent U.S. congressional inquiries and proposed state and federal legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare and reform government program reimbursement methodologies for drug products.

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

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

More recently, with enactment of the Tax Cuts and Jobs Act of 2017, which was signed by the President on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, will become effective in 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. Congress will likely consider other legislation to replace elements of the ACA, during the next Congressional session.

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

Review and Approval of Medicinal Products in the European Union

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, an applicant will need to obtain the necessary approvals by the comparable non-U.S. regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. Specifically, the process governing approval of medicinal products in the European Union, or 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 on June 16, 2014 but is not expected to apply until 2019. 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 (1) a product-specific waiver, (2) a class waiver or (3) a deferral for one or more of the measures included in the PIP.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid across the European Economic Area (i.e., the EU as well as Iceland, Liechtenstein and Norway). Pursuant to Regulation (EC) No 726/2004, the centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy medicinal products, 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 (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the EU when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the EU and that without incentives it is unlikely that the marketing of the drug in the EU would generate sufficient return to justify the necessary investment. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the EU or, if such method exists, the drug will be of significant benefit to those affected by that condition.

Once authorized, orphan medicinal products are entitled to 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, which is commonly referred to as "Brexit". Thereafter, on March 29, 2017, the country formally notified the EU of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. The withdrawal of the United Kingdom from the EU will take effect either on the effective date of the withdrawal agreement or, in the absence of agreement, two years after the United Kingdom provides a notice of withdrawal pursuant to the EU Treaty. Since the regulatory framework for pharmaceutical products in the United Kingdom. covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from EU directives and regulations, Brexit could materially impact the future regulatory regime which applies to products and the approval of product candidates in the United Kingdom. It remains to be seen how, if at all, Brexit will impact regulatory requirements for product candidates and products in the United Kingdom.

Pricing Decisions for Approved Products

In the EU, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies or so-called health technology assessments, in order to obtain reimbursement or pricing approval. For example, the EU provides options for its Member States to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. Member States may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other Member States allow companies to fix their own prices for products, but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the EU have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage health care expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the EU. The downward pressure on health care costs in general, particularly prescription products, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. Political, economic and regulatory developments may further complicate pricing negotiations, and 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-1365 and all of our other preclinical programs for all potential indications. 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, 2017 we had 56 full-time employees, including 29 employees with M.D. or Ph.D. degrees. Of these full-time employees, 44 employees are engaged in research and development activities and 12 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 620 Memorial Drive, Suite 300, Cambridge, Massachusetts 02139, 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 find, copy and inspect information we file at the SEC's public reference room, which is located at 100 F Street, N.E., Room 1580, Washington, DC 20549. Please call the SEC at 1-800-SEC-0330 for more information about the operation of the SEC's public reference room. 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 $29.8 million, $47.7 million and $54.0 million for the years ended December 31, 2015, 2016 and 2017, respectively. As of December 31, 2017, we had an accumulated deficit of $155.3 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 (deficit) 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, and with daratumumab, an anti-CD38 antibody, in a Phase 2 clinical trial, and SY-1365, a selective inhibitor of cyclin-dependent kinase 7, or CDK7, that is currently in the dose-escalation portion of a Phase 1 clinical trial in patients with 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 help us comply with our obligations as a public company; 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, developing our gene control platform and conducting preclinical and early clinical research. We have not yet demonstrated an ability to advance a program into a late-stage clinical trial, obtain marketing approvals, 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 daratumumab, as we develop and seek approval of companion diagnostic tests for use in identifying patients who may benefit from treatment with SY-1425, advance the clinical development of SY-1365 into planned Phase 1 expansion cohorts in ovarian and breast cancers, initiate new research and preclinical development efforts and seek marketing approval for any product candidates that we 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. Furthermore, we expect to incur significant additional costs associated with operating as a public company. 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-1365, 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 existing cash, cash equivalents and marketable securities as of December 31, 2017, together with amounts received from Incyte Corporation, or Incyte, in connection with our collaboration and option agreement executed in January 2018 and the net proceeds from the underwritten public offering of our common stock and concurrent private placement of our common stock to Incyte that closed in February 2018, will enable us to fund our planned operating expense and capital expenditure requirements into 2020. 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-1365 and any associated companion diagnostic tests;
- 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 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 development platform;

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

- our headcount growth and associated costs as we expand our research and development, operate as a public company, and establish a commercial infrastructure;

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

- the costs of operating as a public company.

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 a public offering of our common stock that closed in February 2018, 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, if available, would result in fixed payment obligations and may involve agreements that include 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, 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.

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 late-stage 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 further 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-1365. If we are unable to initiate or complete the clinical development of, obtain marketing approval for or successfully commercialize SY-1425 or SY-1365, 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-1365. 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-1365 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 or SY-1365;
- 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 Co. Ltd., or 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;
- continued availability of appropriate tissue samples to enable the identification of novel targets in genomically defined subsets of patients; 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-1365, 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 newly-diagnosed acute myeloid leukemia, or AML, who are not suitable candidates for standard chemotherapy, and in combination with daratumumab in genomically defined patients with relapsed or refractory AML or higher-risk myelodysplastic syndrome, or MDS, identified using our biomarkers. We anticipate reporting clinical data from this trial in the fourth quarter of 2018. We are collaborating with a third party with respect to the clinical trial assay being used to select patients with our RARA and IRF8 biomarkers for inclusion in the trial. Our anticipated time to data in this trial is subject to our continued ability to initiate clinical trial sites and recruit eligible patients, the performance of the clinical trial assay and the prevalence of patients with these biomarkers, and the satisfaction by biomarker-positive

patients of other eligibility criteria for participation in the trial. 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.

We are also conducting a Phase 1 clinical trial of SY-1365 in patients with advanced solid tumors. We expect to report initial clinical data from the dose escalation portion of this trial in the fourth quarter of 2018. Our anticipated time to data in this trial is subject to our ability to recruit eligible patients and the number of dose cohorts that will need to be enrolled prior to observing pharmacokinetic activity, if achieved at all. Our assumption as to the activity of SY-1365 at particular dose levels may prove to be incorrect. 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 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 stop enrollment 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 and daratumumab. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any. Similarly, in our clinical trials we may fail to detect toxicity of or intolerability caused by our product candidates, or mistakenly believe that our product candidates are toxic or not well tolerated when that is not in fact the case.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us, or any future collaborators, and impair our ability to generate 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-1365 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, our experience administering SY-1365 to humans has been limited to date, so the safety profile that SY-1365 will demonstrate in human clinical trials is unknown. We are and expect to continue evaluating the administration of tamibarotene in combination with other biological and pharmaceutical products, including azacitidine and daratumumab, in patients with AML, MDS and other hematologic malignancies, and we plan to evaluate SY-1365 in combination with a chemotherapeutic agent in patients with ovarian cancer. We cannot predict at this time whether the combination of our product candidates with another product 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 candidate 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 candidate 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 have delays in reaching or fail to reach agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- clinical trials of our product candidates may produce 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 our third-party collaborators in developing and obtaining approval for 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, the diagnostic company with whom we contract may decide 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 diagnostic company may otherwise terminate. We may not be able to enter into arrangements with another diagnostic company 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 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; and
- 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.

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 late-stage clinical trials.

The data supporting our clinical development strategies for SY-1425 and SY-1365 have been derived entirely from preclinical studies. We cannot assure you that we will be able to replicate in human clinical trials the results we observed in animal models. Moreover, the outcome of preclinical studies and early clinical trials may not be predictive of the success of later clinical trials, and interim results of clinical trials do not necessarily predict success in future clinical trials. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials after achieving positive results in earlier development, and we could face similar setbacks. The design of a clinical trial can determine whether its results will support approval of a product and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. We have limited experience in designing clinical trials and may be unable to design and execute a clinical trial to support marketing approval. In addition, preclinical and clinical data are often susceptible to varying interpretations and analyses. Many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval for the product candidates. Even if we, or any 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-1365 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 and managerial 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.

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 in the United States 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.

The development and commercialization of new products is highly competitive. 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 four new drugs approved by the FDA during 2017 for the treatment of AML or patient subsets within AML: midostaurin, enasidanib, daunorubicin + cytarabine liposome, and gemtuzumab. SY-1425 may also face competition from other investigational products currently in clinical development for AML and MDS, including venetoclax, which is currently being evaluated by AbbVie, Inc. in two randomized pivotal studies in patients with AML, as well as investigational products in development from Takeda Pharmaceutical Co. Ltd., Daiichi Sankyo Company, Limited, Agios Pharmaceuticals, Inc., Novartis AG, Bristol-Myers Squibb Co., Eli Lilly & Co., Eisai Inc., Celgene Corporation, Pfizer, Inc., Incyte Corporation and FORMA Therapeutics, LLC. We are aware of only one other selective RARα program, a compound in development from Io Therapeutics, Inc. which, according to a government-sponsored website, is in an investigator initiated Phase 1/2 study in a non-selective patient group in relapsed and refractory AML, high-risk MDS and chronic myelomonocytic leukemia. In addition, we are aware of an oral CDK7 inhibitor being developed by Carrick Therapeutics Ltd. that has recently entered Phase 1 clinical development, and are aware of several other selective CDK7 inhibitor programs that we believe are in preclinical development, including programs from Aurigene Discovery Technologies Ltd., Ube Industries Ltd., Qurient Co. Ltd., and Beta Pharma, Inc. SY-1365 may face competition from these selective CDK7 inhibitors.

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. 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.

Our internal computer systems, or those used by our third-party research institution collaborators, vendors or other contractors or consultants, may fail or suffer security breaches.

Despite the implementation of security measures, our internal computer systems and those of our vendors and other contractors and consultants may be vulnerable to damage from computer viruses and unauthorized access. Although to our knowledge we have not experienced any such material system failure or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations. For example, the loss of clinical trial data from completed, ongoing or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Likewise, we rely on our third-party research institution collaborators for research and development of our product candidates and other third parties for the manufacture of our product candidates and to conduct clinical trials, and similar events relating to their computer systems could also have a material adverse effect on our business. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or systems, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development and commercialization of our product candidates could be delayed.

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.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply for bulk drug substances. 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.

If 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 targets in diseases beyond our current areas of focus, as we have with Incyte in the field of myeloproliferative neoplasms. If and when 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 candidate 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 target discovery collaboration with Incyte contains, 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 its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense.

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 or business, including: a license agreement with Dana-Farber Cancer Institute, or Dana-Farber, under which we were granted an exclusive worldwide license under specified patents relating to CDK7 inhibitors and JNK inhibitors; a license agreement with the Whitehead Institute for Biomedical Research, or Whitehead, and Dana-Farber, pursuant to which we were granted a predominantly exclusive, with certain non-exclusive exceptions, license under specified U.S. patents relating to *MYC* modulators; a license agreement with Whitehead pursuant to which we were granted an exclusive worldwide license under specified patents relating to super-enhancers until April 2016, which license can remain exclusive thereafter, on a field-by-field basis, as long as we can demonstrate that we are using commercially reasonable efforts in the applicable field; and 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 five and ten years, respectively, because 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 licenses from third parties, to develop and commercialize SY-1425 for human cancers in North America and Europe, and SY-1365 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. We are aware of a third party that is offering super-enhancer identification and analysis services, which we believe infringe our issued in-licensed United States patent relating to this subject matter. We are in communication with that third party regarding the timing under which we would grant them a license under our in-licensed patent. If we are unsuccessful in negotiating a license on acceptable terms, we may be required to file infringement claims against that party with all of the associated risks of patent infringement litigation set forth herein. If that party continues to offer these services, it may affect our ability to attract corporate partners who are interested in super-enhancer identification and analysis and may negatively affect the value of our technology platform and therefore harm our business.

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, recent court rulings in cases such as *Association for Molecular Pathology v. Myriad Genetics, Inc.*; *BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litigation*; and *Promega Corp. v. Life Technologies Corp.* 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. On March 29, 2017, the country formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. Since a significant proportion of the regulatory framework in the United Kingdom is derived from European Union directives and regulations, the referendum could materially impact the regulatory regime with respect to the approval of our product candidates in the United Kingdom or the European Union. 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. 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.

Since enactment of the ACA, there have been numerous legal challenges and Congressional actions to repeal and replace provisions of the law. In May 2017, the U.S. House of Representatives passed legislation known as the American Health Care Act of 2017. Thereafter, the Senate Republicans introduced and then updated a bill to replace the ACA known as the Better Care Reconciliation Act of 2017. The Senate Republicans also introduced legislation to repeal the ACA without companion legislation to replace it, and a "skinny" version of the Better Care Reconciliation Act of 2017. In addition, the Senate considered proposed healthcare reform legislation known as the Graham-Cassidy bill. None of these measures was passed by the U.S. Senate.

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

A bipartisan bill to appropriate funds for CSR payments was introduced in the Senate, but the future of that bill is uncertain. More recently, with enactment of the Tax Cuts and Jobs Act of 2017, which was signed by the President on December 22, 2017, Congress repealed the "individual mandate." The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, will become effective in 2019. According to the Congressional Budget Office, the repeal of the individual mandate will cause 13 million fewer Americans to be insured in 2027 and premiums in insurance markets may rise. Further, each chamber of Congress has put forth multiple bills designed to

repeal or repeal and replace portions of the ACA. Although none of these measures has been enacted by Congress to date, Congress may consider other legislation to repeal and replace elements of the ACA. Congress will likely consider other legislation to replace elements of the ACA during the next Congressional session.

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

The costs of prescription pharmaceuticals in the United States has also been the subject of considerable discussion in the United States, and members of Congress and the Administration have stated that they will address such costs through new legislative and administrative measures. The pricing of prescription pharmaceuticals is also subject to governmental control outside the United States. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost effectiveness of our product candidates to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our ability to generate revenues and become profitable could be impaired. In the European Union, similar political, economic and regulatory developments may affect our ability to profitably commercialize our products. In addition to continuing pressure on prices and cost containment measures, legislative developments at the European Union or member state level may result in significant additional requirements or obstacles that may increase our operating costs.

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 our collaborators or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

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

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; [insert name], 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-1365;
- 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 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; and
- the other factors described in this "Risk Factors" section.

Additionally, our stock price is likely to be volatile, and 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 the reduced disclosure requirements applicable to emerging growth 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. 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.

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 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, 2017, we had federal and state net operating loss carryforwards of $136.4 million and $138.8 million, respectively, and federal and state research and development tax credit carryforwards of $6.1 million and $1.8 million, respectively, each of which if not utilized will expire at various dates through 2037. These net operating loss and tax credit carryforwards could expire unused and be unavailable to offset future income tax liabilities. 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. We have not conducted a detailed study to document whether our historical activities qualify to support the research and development credit carryforwards. A detailed study could result in adjustment to our research and development credit carryforwards. 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.

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

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

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 any future debt or credit agreements may preclude us from paying dividends. 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 occupy approximately 21,488 rentable square feet of office and laboratory space in Cambridge, Massachusetts under a lease that expires on October 31, 2020. We have an option to extend the lease term for five additional years. We believe that this 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 The following table sets forth the high and low sales price of our common stock as reported on the Nasdaq Global Select Market for the periods indicated:

	High	Low
Year ended December 31, 2016:		
Second Quarter (beginning June 30, 2016)	$ 19.80	$ 14.58
Third Quarter	$ 21.50	$ 8.16
Fourth Quarter	$ 16.85	$ 11.31
Year ended December 31, 2017:		
First Quarter	$ 16.74	$ 10.22
Second Quarter	$ 19.22	$ 13.27
Third Quarter	$ 24.38	$ 11.21
Fourth Quarter	$ 17.62	$ 6.30

Holders of Our Common Stock

As of February 28, 2018, there were approximately 61 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.

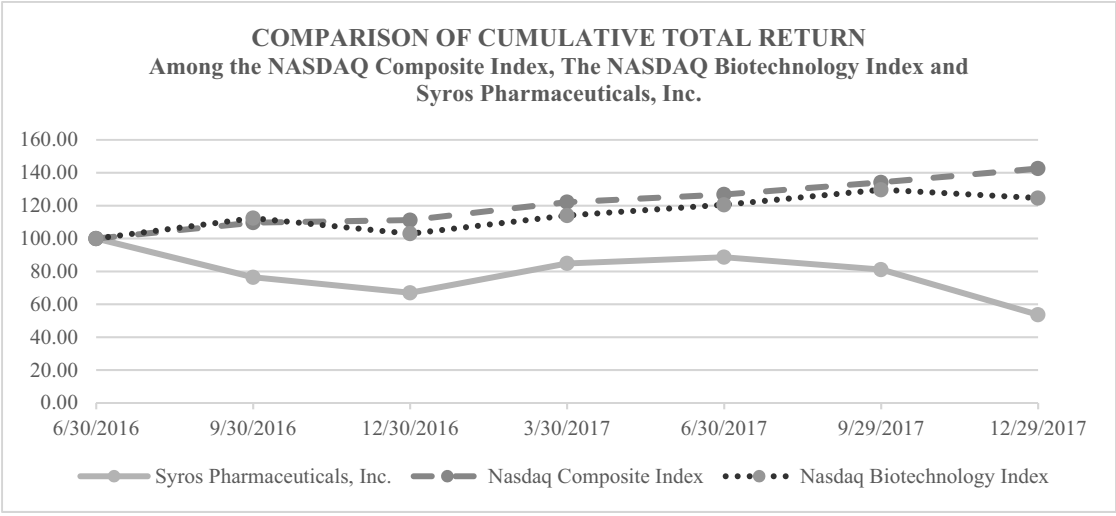
Dividend Policy

We have never declared nor paid cash dividends on our common stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. We do not intend to pay cash dividends in respect of our common stock in the foreseeable future. Any future determination to pay cash dividends will be made at the discretion of our board of directors and will depend on restrictions and other factors our board of directors may deem relevant. Investors should not purchase our common stock with the expectation of receiving cash dividends.

Stock Performance Graph

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

The following graph compares the performance of our common stock to the Nasdaq Composite Index and to the Nasdaq Biotechnology Index from June 30, 2016 (the first date that shares of our common stock were publicly traded) through December 29, 2017, which was the last trading day of the year. The comparison assumes $100 was invested in our common stock and in each of the foregoing indices after the market closed on June 30, 2016, and it assumes reinvestment of dividends, if any. The stock price performance included in this graph is not necessarily indicative of future stock price performance.



Use of Proceeds from Registered Securities

On July 6, 2016, we closed our initial public offering, or our IPO, in which we issued and sold 4,600,000 shares of our common stock at a public offering price of $12.50 per share, including 600,000 shares of common stock sold pursuant to the underwriters' exercise of their option to purchase additional shares of common stock, for aggregate gross proceeds of $57.5 million. All of the shares issued and sold in the IPO were registered under the Securities Act pursuant to a Registration Statement on Form S-1 (File No. 333-211818), which was declared effective by the SEC on June 29, 2016. Cowen and Company, LLC and Piper Jaffray & Co. acted as joint book-running managers of the offering and as representatives of the underwriters. JMP Securities LLC and Wedbush Securities Inc. acted as co-managers for the offering. The offering commenced on June 29, 2016 and did not terminate until the sale of all of the shares offered.

The net offering proceeds to us, after deducting underwriting discounts and offering expenses payable by us totaling $7.6 million, were approximately $49.9 million. No offering expenses were paid directly or indirectly to any of our directors or officers (or their associates) or persons owning 10.0% or more of any class of our equity securities or to any other affiliates.

As of December 31, 2017, we estimate that we have used all of the net proceeds from the IPO to fund manufacturing and clinical development activities for SY-1425, IND-enabling studies and manufacturing activities for SY-1365, and other research activities in support of our preclinical programs and gene control platform, and for working capital and other general corporate purposes.

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 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, 2017, 2016 and 2015 and the consolidated balance sheet data as of December 31, 2017 and 2016 from our audited consolidated financial statements included elsewhere in this Annual Report on Form 10-K. We have derived consolidated statement of operations data for the years ended December 31, 2014 and 2013, and consolidated balance sheet data as of December 31, 2015 and 2014 from our audited consolidated financial statements and related notes 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				
	2017	2016	2015	2014	2013
	(in thousands, except for per share data)				
Statements of operations data:					
Revenue	$ 1,101	$ 317	$ 317	$ —	$ —
Operating expenses:					
Research and development	41,896	$ 37,817	$ 24,408	10,923	6,266
General and administrative	13,891	$ 10,463	$ 5,729	2,512	2,367
Total operating expenses	55,787	48,280	30,137	13,435	8,633
Loss from operations	(54,686)	(47,963)	(29,820)	(13,435)	(8,633)
Other income (expense), net	676	$ 220	$ 2	4	(32)
Net loss	$ (54,010)	$ (47,743)	$ (29,818)	$ (13,431)	$ (8,665)
Net loss per share applicable to common stockholders - basic and diluted (1)	$ (2.13)	$ (4.05)	$ (17.55)	$ (10.26)	$ (8.45)
Weighted-average number of common shares used in net loss per share applicable to common stockholders - basic and diluted (1)	25,406,845	12,696,414	1,980,286	1,525,018	1,095,973

	As of December 31,			
	2017	2016	2015	2014
	(in thousands)			
Balance sheet data:				
Cash, cash equivalents and marketable securities	$ 72,049	$ 83,593	$ 35,909	$ 60,393
Working capital (2)	60,746	75,941	28,493	59,291
Total assets	78,488	91,323	43,631	61,494
Convertible preferred stock (3)	—	—	82,013	82,013
Total stockholders' equity (deficit)	65,324	80,602	(47,964)	(21,772)

(1) See Note 2 to our consolidated financial statements 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 for further details regarding our current assets and current liabilities.

(3) On July 6, 2016, upon the closing of our IPO, all of the then-outstanding shares of our convertible preferred stock converted into 15,988,800 shares of common stock.

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, 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 pioneering an understanding of the non-coding regulatory region of the genome controlling the activation and repression of genes. Our goal is to advance a new wave of medicines to control the expression of genes. We have built a proprietary gene control platform designed to systematically and efficiently analyze this unexploited region of DNA in human disease tissue to identify novel targets linked to genomically defined patient populations and to develop drugs against those targets based on our expertise in transcriptional chemistry. Because gene expression is fundamental to the function of all cells, we believe that our gene control platform has broad potential to create medicines that achieve profound and durable benefit across therapeutic areas and a range of diseases. We are currently focused on developing treatments for cancer and diseases resulting from modifications of a single gene, also known as monogenic diseases, and are 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 being evaluated in combination with azacitidine, a hypomethylating agent frequently used to treat acute myeloid leukemia, or AML, and myelodysplastic syndrome, or MDS, patients, and with daratumumab, an anti-CD38 therapeutic antibody approved to treat multiple myeloma, in a Phase 2 clinical trial in genomically defined subsets of patients with AML and MDS; and

- SY-1365, a selective inhibitor of cyclin-dependent kinase 7, or CDK7, in a Phase 1 clinical trial in patients with advanced solid tumors for which expansions in ovarian and breast cancer are planned.

We also have multiple programs in earlier stages of research and development in oncology, including immuno-oncology, and monogenic diseases. Our goal is to build a fully integrated biopharmaceutical company based on our leadership position in gene control.

At the 59th American Society of Hematology Annual Meeting and Exposition in December 2017, or ASH 2017, we presented clinical data from our Phase 2 clinical trial evaluating SY-1425 as a single agent in defined subsets of AML and MDS patients with our proprietary *RARA* and *IRF8* biomarkers. In 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 and that clinical and biological activity was observed in patients enrolled in the trial. Specifically, clinical activity was observed in ten of 23 (43%) evaluable patients with relapsed or refractory AML and higher-risk MDS, including improvement in blood counts, reduction in leukemic blasts and one bone marrow complete response. Thirteen of the 23 (57%) evaluable relapsed or refractory AML and higher-risk MDS patients had stable disease. Myeloid differentiation was also observed in the bone marrow, consistent with the underlying mechanism of action of SY-1425 as a differentiating agent. Induction of CD38, a marker of cell differentiation, was observed after one 28-day cycle of treatment in 11 of 13 (85%) patients with pre- and post-treatment immunophenotyping samples.

We believe that these clinical data, when combined with preclinical data showing the tumor-killing activity of SY-1425 in combination with azacitidine and with daratumumab support the ongoing development of SY-1425 as a combination agent. SY-1425 has shown synergistic tumor-killing activity in combination with azacitidine as well as with daratumumab in preclinical models of *RARA* biomarker-positive AML. In combination with azacitidine, SY-1425 demonstrated greater clearance of tumor cells in bone marrow and other tissues and greater depth and duration of tumor response in preclinical models, compared to either azacitidine or SY-1425 alone. In combination with daratumumab, SY-1425 induced robust immune cell-mediated tumor death *in vitro*. Notably, AML cells do not normally express high

levels of CD38. We have shown that by inducing CD38 expression, SY-1425 sensitizes biomarker-positive AML models to the tumor-killing effects of daratumumab.

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 not suitable candidates for standard chemotherapy and in combination with daratumumab in approximately 12 relapsed or refractory AML and higher-risk MDS patients. All patients enrolled or to be enrolled in the trial have been or will be prospectively selected using our proprietary *RARA* or *IRF8* biomarkers. In December 2017, we entered into a clinical supply agreement with Janssen Research and Development, LLC, or Janssen, pursuant to which Janssen agreed to supply us daratumumab for use in the trial. We are no longer dosing patients in the cohorts of the trial in which SY-1425 was being evaluated as a single agent. We expect to report initial clinical data from the combination cohorts of the trial in the fourth quarter of 2018.

We are continuing to dose patients in the dose-escalation phase of our ongoing Phase 1 clinical trial of SY-1365 and expect to report data from this phase of the trial in the fourth quarter of 2018. Once a maximum tolerated dose is reached in the dose escalation phase of the Phase 1 clinical trial and the recommended dosing schedule is identified, we intend to open expansion cohorts evaluating SY-1365 in multiple ovarian cancer populations as a single agent as well as in combination with carboplatin, a chemotherapeutic agent. The ovarian cancer populations include a 24-patient cohort evaluating SY-1365 as a single agent in patients who have relapsed after three or more prior therapies, a 24-patient cohort evaluating SY-1365 in combination with carboplatin in patients who relapsed after one or more prior therapies but who may still benefit from additional platinum-based treatment, and a 12-patient pilot cohort evaluating SY-1365 as a single agent in primary platinum-refractory disease. We also plan to evaluate SY-1365 in combination with fulvestrant, a hormonal medicine, in 12 patients with hormone-receptor positive, HER-2 negative metastatic breast cancer who have progressed after treatment with a CDK4/6 inhibitor plus an aromatase inhibitor. We also plan to evaluate the mechanism of action of SY-1365 in ten patients with any solid tumor accessible for biopsies. We expect that the expansion cohorts in our Phase 1 clinical trial will be open to enrollment in mid-2018.

We currently have five programs in our preclinical and discovery pipeline, including preclinical programs directed to the development of a CDK7 inhibitor that can be administered orally, inhibitors of cyclin-dependent kinase 12/13, and inhibitors of an immuno-oncology target, as well as discovery programs related to a gene control target to treat sickle cell disease and in the field of cancer. We plan to nominate a development candidate from one of these programs during 2018 that we can advance into preclinical studies to support a potential investigational new drug application, or IND, filing in 2019. We have and are continuing to 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 a target discovery, research collaboration and option agreement with Incyte Corporation, or Incyte, in January 2018 under which we will use our platform to identify novel therapeutic targets with a focus on myeloproliferative neoplasms.

Recent Developments

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 will receive 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. Incyte will have exclusive worldwide rights to develop and commercialize any therapies under the collaboration that modulate those validated targets.

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. Our activities under this agreement are subject to a joint research plan and, subject to certain exceptions, Incyte will be responsible for funding our activities under the research plan, including amounts in excess of the pre-paid research funding amount. 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 option 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.

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 gross proceeds to us of $1.4 million.

Public Offering

On January 30, 2018, we issued and sold an aggregate of 4,188,481 shares of our common stock in a public offering at a price per share $9.55 per share, resulting in gross proceeds of $40.0 million before deducting underwriting commissions and fees estimated to be approximately $2.7 million. Additionally, on February 2, 2018, the underwriters exercised their option to purchase an additional 628,272 shares at a price per share of $9.55, resulting in additional gross proceeds of $6.0 million.

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. Our only source of revenue to date has been a research agreement with a multinational pharmaceutical company. For the year ended December 31, 2017 and 2016, we recognized $1.1 million and $0.3 million, respectively, in revenue related to this agreement. This research agreement expired on March 31, 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 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 years ended December 31, 2017 and 2016 (in thousands):

	Year Ended December 31,	
	2017	2016
SY-1425 external costs	$ 9,227	$ 7,940
SY-1365 and other CDK7 program external costs	8,289	8,129
Other research and platform programs external costs	8,161	7,184
Employee-related expenses, including stock-based compensation	11,719	11,214
Facilities and other expenses	4,500	3,350
Total research and development expenses	$ 41,896	$ 37,817

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 an IND and minimally efficacious dose studies in animals, where applicable and requested under the good laboratory practice, or GLP, requirements of the FDA;
- 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 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. We also anticipate that we will incur increased accounting, audit, legal, compliance and director and officer insurance costs, as well as investor and public relations expenses, associated with operating as a public company.

Other Income, Net

Other income, net consists of interest income on our cash and cash equivalents, interest, dividends, amortization of premiums and discounts, realized gains and losses on sales of marketable securities and interest expense related to our equipment financing arrangement.

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

We recognize revenue in accordance with Financial Accounting Standards Board, or FASB, Accounting Standards Codification, or ASC, Topic 605 Revenue Recognition, or ASC 605. Accordingly, revenue is recognized for each unit of accounting when all of the following criteria are met:

- persuasive evidence of an arrangement exists;
- delivery has occurred or services have been rendered;
- the seller's price to the buyer is fixed or determinable; and
- collectability is reasonably assured.

We analyze multiple element arrangements based on the guidance in ASC Topic 605-25, Revenue Recognition—Multiple Element Arrangements, or ASC 605-25. Pursuant to the guidance in ASC 605-25, we evaluate 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 involves subjective determinations and we are required to make judgements about the individual deliverables and whether such deliverables are separate from other aspects of the contractual relationship. Deliverables are considered separate units of accounting provided that: (i) the delivered item(s) has value to the customer on a standalone basis and (ii) the arrangement includes a general right of return relative to the delivered item(s), delivery or performance of the undelivered item(s) is considered probable and substantially within our control.

We recognize arrangement consideration allocated to each unit of accounting when all of the revenue recognition criteria in ASC 605 are satisfied for that particular unit of accounting. In the event that a deliverable does not represent a separate unit of accounting, we recognize revenue from the combined unit of accounting over the contractual or estimated performance period for the undelivered items, which is typically the term of our research and development obligations. If there is no discernible pattern of performance or objectively measurable performance measures do not exist, then we recognize revenue under the arrangement on a straight-line basis over the period we are expected to complete our performance obligations or upon completion when the final act is of such significance to the overall arrangement that performance has not substantively occurred until the completion of that act. Conversely, if the pattern of performance over which the service is provided to the customer can be determined and objectively measurable performance measures exist, then we recognize revenue under the arrangement using the proportional performance method.

The research agreement we entered with a multinational pharmaceutical company contained a single unit of accounting and we recognized service revenue based upon the completed performance method of revenue recognition as we are unable to reasonably estimate the period of performance of the services and the delivery of the final study report was significant to the arrangement.

Research and Development Expenses

As part of the process of preparing our financial statements, we are required to estimate our accrued expenses as of each balance sheet date. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed or when contractual milestones are met. We make estimates of our accrued expenses as of each balance sheet date based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our estimates with the service providers and make adjustments if necessary. The significant estimates in our accrued research and development expenses include the costs incurred for services performed by our service providers in connection with research and development activities for which we have not yet been invoiced.

We record our expenses related to research and development activities based on our estimates of the services received and efforts expended pursuant to contracts with vendors that conduct research and development on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the research and development expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid accordingly. Non-refundable advance payments for goods and services that will be used in future 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.

Although we do not expect our estimates to be materially different from amounts actually incurred, if our estimates of the status and timing of services performed differ from the actual status and timing of services performed, it could result in us reporting amounts that are too high or too low in any particular period. To date, there have been no material differences between our estimates of such expenses and the amounts actually incurred.

We have and may in the future 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 apply the fair value recognition provisions of ASC Topic 718, Compensation—Stock Compensation, or ASC 718. Determining the amount of stock-based compensation to be recorded requires us to develop estimates of the fair value of stock options as of their grant date. Calculating the fair value of stock-based awards requires that we make highly subjective assumptions.

We use the Black-Scholes option pricing model to value our stock option awards. Use of this valuation methodology requires that we make assumptions as to the volatility of our common stock, the expected term of our stock options, the risk free interest rate for a period that approximates the expected term of our stock options and our expected dividend yield. Prior to June 30, 2016, we were a privately-held company and lacked company-specific historical and implied volatility information. As such, we utilize data from a representative group of public companies to estimate expected stock price volatility. For purposes of identifying representative companies, we considered characteristics such as number of product candidates in early stages of product development, area of therapeutic focus, length of trading history and similar vesting provisions. The expected volatility was determined using an average of the historical volatilities of the representative group of companies for a period equal to the expected term of the option grant. We intend to consistently apply this process using the same representative companies until a sufficient amount of historical information regarding the volatility of our own share price becomes available or until circumstances change, such that the identified entities are no longer representative companies. In the latter case, more suitable, similar entities whose share prices are publicly available would be utilized in the calculation.

We use the ‘‘simplified method’’ to estimate the expected term of stock option grants to employees. Under this approach, the weighted-average expected option term is presumed to be the average of the contractual term (ten years) and the vesting term (generally four years) of our stock options. We utilize this method due to lack of historical exercise data and the ‘‘plain-vanilla’’ nature of our stock-based awards. The risk-free rate is based on the yield curve of U.S. Treasury securities in effect at the time of grant with periods commensurate with the expected term of the options being valued. We have never paid, and do not anticipate paying, any cash dividends in the foreseeable future, and therefore use an expected dividend yield of zero in the option-pricing model.

Prior to becoming a public company, we determined the fair value of our common stock using the option pricing method, or OPM, or a hybrid of the probability-weighted expected return method and OPM. The fair value of our common stock underlying our stock-based awards was determined on each grant date by our board of directors. Upon becoming a public company, the fair value of the underlying shares of common stock equals the closing price of our stock on The Nasdaq Global Select Market on the date of grant.

The amount of stock-based compensation expense recognized is based on the fair value of the award on the date of grant. As a result of the adoption of ASU 2016-09, effective January 1, 2017, we account for forfeitures as they occur instead of estimating forfeitures at the time of grant and revising those estimates in subsequent periods if actual forfeitures differ from its estimates. Ultimately, the actual expense recognized over the vesting period will be for only those options that vest.

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

	Year Ended December 31,		
	2017	2016	2015
Weighted-average risk-free interest rate	2.07 %	1.36 %	1.78 %
Expected dividend yield	— %	— %	— %
Expected option term	6.05	5.98	6.09
Volatility	87.83 %	85.39 %	82.71 %

We expense the fair value of our stock-based awards to employees on a straight-line basis over the associated service period, which is generally the vesting period. For stock-based awards granted to consultants and non-employees, we recognize compensation expense over the period during which the services are rendered by such consultants and non-employees. At the end of each financial reporting period prior to completion of the service, the fair value of these awards is remeasured using the then-current fair value of our common stock for restricted stock and updated assumptions in the Black-Scholes option-pricing model for stock options.

We record the expense for stock-based awards that contain performance-based milestones 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 are probable, in which case expense is accelerated.

Results of Operations

Comparison of Years Ended December 31, 2017 and 2016

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

	Year Ended December 31,			
	2017	2016	Dollar Change	% Change
Statements of Operations Data:				
Revenue	$ 1,101	$ 317	$ 784	247 %
Operating expenses:				
Research and development	41,896	37,817	4,079	11 %
General and administrative	13,891	10,463	3,428	33 %
Total operating expenses	55,787	48,280	7,507	16 %
Other income, net	676	220	456	207 %
Net loss	$ (54,010)	$ (47,743)	$ 6,267	13 %

Revenue

In November 2014, we entered into a research agreement with a multinational pharmaceutical company for purposes of mapping immune cell super-enhancers and transcriptional targets in autoimmune disease. Under the research agreement, we were responsible for the conduct of all activities under separate projects, as defined in the research agreement. We recognized revenue on a completed performance basis for each project performed under the agreement. We recognized revenue of $1.1 million and $0.3 million during the years ended December 31, 2017 and December 31, 2016, respectively. The agreement with the multinational pharmaceutical company expired on March 31, 2017 in accordance with its terms.

Research and Development Expense

Research and development expense increased by approximately $4.1 million, or 11%, from $37.8 million for the year ended December 31, 2016 to $41.9 million for the year ended December 31, 2017. The following table summarizes our research and development expenses for the years ended December 31, 2017 and 2016, together with the changes to those items in dollars (in thousands):

	Year Ended December 31,			
	2017	2016	Dollar Change	% Change
External research and development	$ 23,785	$ 20,802	$ 2,983	14 %
Employee-related expenses, excluding stock-based compensation	10,053	8,234	1,819	22 %
Stock-based compensation	1,666	2,980	(1,314)	(44)%
Consulting, licensing and professional fees	1,892	2,451	(559)	(23)%
Facilities and other expenses	4,500	3,350	1,150	34 %
Total research and development expenses	$ 41,896	$ 37,817	$ 4,079	11 %

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 $3.0 million, or 14%, for expenses from third parties that conduct research and development and preclinical activities on our behalf, including an increase of approximately $5.5 million in clinical development for SY-1425 and SY-1365, offset by a decrease of $2.2 million in preclinical development work for SY-1365 as toxicology studies were completed and the Phase 1 clinical trial was initiated;

- an increase of approximately $1.8 million, or 22%, for increased personnel related expenses, including increased salary and benefits primarily due to the hire of key research and development personnel;

- a decrease of approximately $1.3 million, or 44%, for decreased stock-based compensation expense primarily related to the recognition of expense related to performance triggers achieved during 2016 for which no corresponding expense was recognized during 2017;

- a decrease of approximately $0.6 million, or 23% in consulting, licensing, and professional fees, due to the $0.5 million license payment paid to TMRC Co., Ltd., or TMRC, in 2016 under our license agreement with TMRC, which we refer to as the TMRC license agreement; and

- an increase of approximately $1.2 million, or 34%, for increases in the proportion of costs allocated to research and development, as well as increases in facilities costs including depreciation and maintenance expenses associated with our operating lease at our corporate headquarters beginning in August 2015.

General and Administrative Expense

General and administrative expense increased by approximately $3.4 million, or 33% from $10.5 million for the year ended December 31, 2016 to $13.9 million for the year ended December 31, 2017. The change in general and administrative expense was primarily attributable to an increase in employee-related costs, including salary, benefits and stock-based compensation, as well as increased consulting, licensing, and professional fees to support our overall growth as a company.

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, and interest expense related to our equipment financing arrangement. The increase in other income from the year ended December 31, 2016 to the year ended December 31, 2017 is due to a full year of investing activities in 2017, as we started investing in marketable securities beginning in October 2016.

Comparison of Years Ended December 31, 2016 and 2015

The following table summarizes our results of operations for the years ended December 31, 2016 and 2015, together with the changes in those items in dollars (in thousands):

	Year Ended December 31,			
	2016	2015	Dollar Change	Dollar Change
Statements of Operations Data:				
Revenue	$ 317	$ 317	$ —	— %
Operating expenses:				
Research and development	37,817	24,408	13,409	55 %
General and administrative	10,463	5,729	4,734	83 %
Total operating expenses	48,280	30,137	18,143	60 %
Other income, net	220	2	218	10,900 %
Net loss	$ (47,743)	$ (29,818)	$ 17,925	60 %

Revenue

In November 2014, we entered into a research agreement with a multinational pharmaceutical company for purposes of mapping immune cell super-enhancers and transcriptional targets in autoimmune disease. Under the research agreement, we were responsible for the conduct of all activities under separate projects, as defined in the research agreement. We recognized revenue on a completed performance basis for each project performed under the agreement. We recognized revenue of $0.3 million during each of the years ended December 31, 2016 and December 31, 2015.

Research and Development Expense

Research and development expense increased by approximately $13.4 million, or 55%, from $24.4 million for the year ended December 31, 2015 to $37.8 million for the year ended December 31, 2016. The following table summarizes our research and development expenses for the year ended December 31, 2016 and 2015, together with the changes to those items in dollars (in thousands):

	Year Ended December 31,			
	2016	2015	Dollar Change	% Change
External research and development	$ 20,802	$ 12,749	$ 8,053	63 %
Employee-related expenses, excluding stock-based compensation	8,234	5,344	2,890	54 %
Stock-based compensation	2,980	2,733	247	9 %
Consulting, licensing and professional fees	2,451	1,972	479	24 %
Facilities and other expenses	3,350	1,610	1,740	108 %
Total research and development expenses	$ 37,817	$ 24,408	$ 13,409	55 %

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

- an increase of approximately $8.1 million, or 63% for expenses from third parties that conduct research and development and preclinical activities on our behalf, including approximately $6.1 million in contract manufacturing and clinical development for SY-1425, a $1.0 million milestone payment made under our license agreement with TMRC in September 2016, and approximately $0.9 million for preclinical development for SY-1365 and advancement of the CDK7 program;

- an increase of approximately $2.9 million, or 54% for increased personnel related expenses, including increased salary and benefits primarily due to the hire of research and development personnel;

- an increase of approximately $0.2 million, or 9% for increased stock-based compensation expense;

- an increase of approximately $0.5 million, or 24% in consulting, licensing, and professional fees, due to increased preclinical, clinical and regulatory consulting fees for SY-1425 and SY-1365; and

- an increase of approximately $1.7 million, or 108% for increases in facilities costs including depreciation and maintenance expenses associated with our operating lease at our corporate headquarters beginning in August 2015.

General and Administrative Expense

General and administrative expense increased by approximately $4.7 million, or 83% from $5.7 million for the year ended December 31, 2015 to $10.5 million for the year ended December 31, 2016. The change in general and administrative expense was primarily attributable to an increase in employee-related costs, including salary, benefits and stock-based compensation, as well as increased consulting, licensing, and professional fees, including increased

corporate legal fees in support of the negotiations of the TMRC license agreement and the negotiations of our operating lease agreement for office space and increased public relations expenses.

Other Income, Net

Other income, net consists of interest income on our cash, cash equivalents and marketable securities, offset by interest expense related to our equipment financing arrangement. The increase in other income from the year ended December 31, 2015 to the year ended December 31, 2016 is due to a higher level of invested cash and cash equivalents from our proceeds.

Liquidity and Capital Resources

Sources of Liquidity

We funded our operations from inception through December 31, 2017 primarily through gross proceeds of $122.2 million from sales of our preferred stock and the issuance of convertible notes that subsequently converted into preferred stock, $57.5 million in gross proceeds from the sale of common stock in our initial public offering, or IPO, and $35.0 million in gross proceeds from the sale of common stock in a private placement in April 2017.

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. Further, in July 2017, we entered into a sales agreement with Cowen and Company, LLC, or Cowen, pursuant to which, from time to time, 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.

As of December 31, 2017, we had cash, cash equivalents and marketable securities of approximately $72.0 million.

Cash Flows

The following table provides information regarding our cash flows for the years ended December 31, 2017, 2016 and 2015 (in thousands):

	Year Ended December 31,		
	2017	2016	2015
Net cash provided by (used in):			
Operating activities	$ (44,729)	$ (40,536)	$ (23,030)
Investing activities	(15,591)	(27,342)	(1,176)
Financing activities	33,937	90,557	(278)
Net increase (decrease) in cash and cash equivalents	$ (26,383)	$ 22,679	$ (24,484)

Net Cash Used in Operating Activities

The use of cash in all periods 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 $44.7 million during the year ended December 31, 2017 compared to $40.5 million during the year ended December 31, 2016. The increase in cash used in operating activities was primarily due to an increase in our net loss of $6.3 million for the year ended December 31, 2017 as compared to the year ended December 31, 2016.

Net cash used in operating activities was $40.5 million during the year ended December 31, 2016 compared to $23.0 million during the year ended December 31, 2015. The increase in cash used in operating activities was primarily due to an increase in net loss of $17.9 million for the year ended December 31, 2016 as compared to the year ended December 31, 2015.

Net Cash Used in Investing Activities

Net cash used in investing activities was $15.6 million during the year ended December 31, 2017 compared to $27.3 million during the year ended December 31, 2016. The decrease in cash used in investing activities was primarily due to sales and maturities of marketable securities of $27.0 million during 2017 compared to no sales or maturities of marketable securities during 2016, offset by an increase in purchases of marketable securities during 2017.

Net cash used in investing activities was $27.3 million during the year ended December 31, 2016 compared to $1.2 million during the year ended December 31, 2015. The increase in cash used in investing activities was due to purchases of marketable securities as well as increased purchases of property and equipment associated with our corporate headquarters.

Net Cash Provided by (Used in) Financing Activities

Net cash provided by financing activities was $33.9 million during the year ended December 31, 2017, compared to net cash provided by financing activities of $90.6 million during the year ended December 31, 2016. The decrease in cash provided by financing activities is primarily due to the issuance of common stock in connection with the IPO in July 2016, as well as the issuance of $39.8 million in a preferred stock financing in January 2016, offset by gross proceeds of $35.0 million in connection with the sale of common stock through private placement in April 2017.

Net cash provided by financing activities was $90.6 million during the year ended December 31, 2016 compared to net cash used in financing activities of $0.3 million during the year ended December 31, 2015. The increase in cash provided by financing activities was primarily due to the issuance of common stock in connection with the IPO in July 2016, as well as the issuance of $39.8 million in a preferred stock financing in January 2016.

Funding Requirements

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue clinical trials of SY-1425 and SY-1365, seek to develop companion diagnostic tests for use with our product candidates, initiate new research and preclinical development efforts 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. Furthermore, we expect to incur additional costs associated with operating as a public company. 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 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, 2017, together with amounts received from Incyte in connection with our collaboration and option agreement executed in January 2018 and the net proceeds from the underwritten public offering of our common stock and concurrent private placement of our common stock to Incyte that closed in February 2018, will enable us to fund our planned operating expense and capital expenditure requirements into 2020. Our future capital requirements will depend on many factors, including:

- the scope, progress, timing, costs and results of clinical trials of SY-1425 and SY-1365 and any associated companion diagnostic tests;
- research and preclinical development efforts for any future product candidates that we may develop;
- our ability to enter into and the terms and timing of any collaborations, licensing agreements or other arrangements;
- whether our 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 number of future product candidates that we pursue and their development requirements;
- 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 development platform;
- revenue received from commercial sales, if any, of our current and future product candidates;
- our headcount growth and associated costs as we expand our research and development, operate as a public company, and establish a commercial infrastructure;
- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights and defending against intellectual property related claims; and
- the costs of operating as a public company.

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.

Contractual Obligations and Commitments

As December 31, 2017, we have a capital lease for laboratory equipment that expires in March 2018 and a capital lease for office equipment that ends in April 2020. Additionally, we lease office space at 620 Memorial Drive in Cambridge, Massachusetts under a non-cancellable operating lease that expires in October 2020. The following table summarizes our significant contractual obligations as of payment due date by period at December 31, 2017:

	Payments due by period				
(in thousands)	Total	Less than 1 year	1 to 3 years	3 to 5 years	More than 5 years
Capital lease payments	$ 55	$ 48	$ 7	$ —	$ —
Operating lease payments	3,743	1,288	2,455	—	—
Total	$ 3,798	$ 1,336	$ 2,462	$ —	$ —

We enter into agreements in the normal course of business with our contract research organizations and institutions to license intellectual property. We have not included these future payments in the table of contractual obligations above since the contracts are cancelable at any time by us, generally upon 30 to 90 days prior written notice.

Our license agreements include potential milestone payments that are contingent upon the successful development and commercialization of products using the intellectual property licensed under such agreements. Under our agreements with Dana-Farber and Whitehead, the maximum aggregate potential milestone payments payable by us total approximately $6.9 million. Under the applicable agreement, we are also required to pay annual maintenance fees, as well as tiered, single digit percentage royalties, on a country-by-country, product-by-product basis, on net product sales.

Under the amended and restated TMRC license agreement, we may make additional payments upon the successful achievement of pre-specified clinical and regulatory milestones in an aggregate amount of approximately $13.0 million per indication. In May 2016, we paid TMRC $0.5 million representing the balance of the remaining upfront license fee and in September 2016, we made a $1.0 million milestone payment to TMRC upon the successful dosing of the first patient in our Phase 2 clinical trial of SY-1425.

We also entered into a supply arrangement with TMRC, under which the Company agreed to pay TMRC a fee for each kilogram of SY-1425 active pharmaceutical ingredient that is produced. During the year ended December 31, 2017, we paid TMRC $0.4 million in payments related to this agreement. No payments were made under this supply management arrangement during the year ended December 31, 2016.

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 $1.0 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 a money market fund and marketable securities and are invested in U.S. Treasury 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, 2017, we had minimal or no 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, 2017.

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, 2017 and 2016, the related consolidated statements of operations, comprehensive loss, convertible preferred stock and stockholders' equity (deficit) and cash flows for each of the three years in the period ended December 31, 2017, 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, 2017 and 2016, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2017, in conformity with US generally accepted accounting principles.

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 12, 2018

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

	December 31, 2017	December 31, 2016
Assets		
Current assets:		
Cash and cash equivalents	$ 32,205	$ 58,588
Marketable securities	39,844	25,005
Accounts receivable	—	867
Prepaid expenses and other current assets	917	1,048
Restricted cash	193	—
Total current assets	73,159	85,508
Property and equipment, net	3,938	4,850
Other long-term assets	1,101	482
Restricted cash	290	483
Total assets	$ 78,488	$ 91,323
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 2,283	$ 2,415
Accrued expenses	9,728	6,115
Deferred revenue	—	550
Deferred rent, current portion	355	319
Capital lease obligations, current portion	47	168
Total current liabilities	12,413	9,567
Deferred rent, net of current portion	745	1,101
Capital lease obligations, net of current portion	6	53
Commitments and contingencies (Note 9)		
Stockholders' equity:		
Preferred stock, $0.001 par value; 10,000,000 shares authorized at December 31, 2017 and December 31, 2016, 0 shares issued and outstanding at December 31, 2017 and December 31, 2016	—	—
Common stock, $0.001 par value; 200,000,000 shares authorized at December 31, 2017 and December 31, 2016; 26,423,375 and 23,380,888 shares issued and outstanding at December 31, 2017 and December 31, 2016, respectively	26	23
Additional paid-in capital	220,606	181,844
Accumulated other comprehensive loss	(42)	(9)
Accumulated deficit	(155,266)	(101,256)
Total stockholders' equity	65,324	80,602
Total liabilities and stockholders' equity	$ 78,488	$ 91,323

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,		
	2017	**2016**	**2015**
Revenue	$ 1,101	$ 317	$ 317
Operating expenses:			
Research and development	41,896	37,817	24,408
General and administrative	13,891	10,463	5,729
Total operating expenses	55,787	48,280	30,137
Loss from operations	(54,686)	(47,963)	(29,820)
Other income, net	676	220	2
Net loss	$ (54,010)	$ (47,743)	$ (29,818)
Accrued dividends on preferred stock	—	(3,681)	(4,934)
Net loss applicable to common stockholders	$ (54,010)	$ (51,424)	$ (34,752)
Net loss per share applicable to common stockholders - basic and diluted	$ (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	25,406,845	12,696,414	1,980,286

See accompanying notes to consolidated financial statements.

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

	Year Ended December 31,		
	2017	2016	2015
Net loss	$ (54,010)	$ (47,743)	$ (29,818)
Other comprehensive loss:			
Unrealized holding losses on marketable securities	(33)	(9)	—
Comprehensive loss	$ (54,043)	$ (47,752)	$ (29,818)

See accompanying notes to consolidated financial statements.

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

	Series A Convertible Preferred Stock		Series B Convertible Preferred Stock		Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Stockholders' (Deficit) Equity
	# of Shares	Amount	# of Shares	Amount	# of Shares	Par Value				
Balance at December 31, 2014	30,350,000	$ 29,015	16,893,931	$ 52,998	1,640,009	$ 1	$ 1,922	$ —	$ (23,695)	$ (21,772)
Exercise of stock options and vesting of restricted stock awards	—	—	—	—	723,009	1	392	—	—	393
Stock-based compensation expense	—	—	—	—	—	—	3,233	—	—	3,233
Net loss	—	—	—	—	—	—	—	—	(29,818)	(29,818)
Balance at December 31, 2015	30,350,000	29,015	16,893,931	52,998	2,363,018	2	5,547	—	(53,513)	(47,964)
Issuance of Series B convertible preferred stock, net of issuance costs of $206	—	—	12,714,150	39,794	—	—	—	—	—	—
Conversion of Series A convertible preferred stock into common stock	(30,350,000)	(29,015)	—	—	8,093,326	8	29,007	—	—	29,015
Conversion of Series B convertible preferred stock into common stock	—	—	(29,608,081)	(92,792)	7,895,474	8	92,784	—	—	92,792
Exercise of stock options and vesting of restricted stock awards	—	—	—	—	429,070	—	395	—	—	395
Issuance of common stock under initial public offering, net of issuance costs of $7.6 million	—	—	—	—	4,600,000	5	49,877	—	—	49,882
Stock-based compensation expense	—	—	—	—	—	—	4,234	—	—	4,234
Other comprehensive loss	—	—	—	—	—	—	—	(9)	—	(9)
Net loss	—	—	—	—	—	—	—	—	(47,743)	(47,743)
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 $2.4 million	—	—	—	—	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

See accompanying notes to consolidated financial statements.

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

	Year Ended December 31,		
	2017	2016	2015
Operating activities			
Net loss	$ (54,010)	$ (47,743)	$ (29,818)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	1,527	1,273	602
Loss on disposal of assets	—	4	17
Stock-based compensation expense	4,419	4,234	3,233
Net amortization of premiums and discounts on marketable securities	(102)	6	—
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	131	(508)	(390)
Accounts receivable	867	(317)	—
Other long-term assets	(365)	(482)	—
Restricted cash	—	—	(413)
Accounts payable	141	(404)	2,022
Accrued expenses	3,533	3,685	1,663
Deferred revenue	(550)	—	—
Deferred rent and lease incentive	(320)	(284)	54
Net cash used in operating activities	(44,729)	(40,536)	(23,030)
Investing activities			
Purchases of property and equipment	(821)	(2,322)	(1,176)
Purchases of marketable securities	(41,770)	(25,020)	—
Sales or maturities of marketable securities	27,000	—	—
Net cash used in investing activities	(15,591)	(27,342)	(1,176)
Financing activities			
Payments on capital lease obligations	(168)	(135)	(50)
Proceeds from issuance of common stock through employee benefit plans	1,799	395	392
Proceeds from issuance of convertible preferred stock, net of issuance costs	—	39,813	—
Proceeds from issuance of common stock, net of issuance costs	32,306	50,484	(620)
Net cash provided by (used in) financing activities	33,937	90,557	(278)
(Decrease) increase in cash and cash equivalents	(26,383)	22,679	(24,484)
Cash and cash equivalents			
Beginning of period	58,588	35,909	60,393
End of period	$ 32,205	$ 58,588	$ 35,909
Supplemental disclosure of cash flow information:			
Cash paid for interest	$ 9	$ 19	$ 18
Non-cash investing and financing activities			
Conversion of convertible preferred stock into common stock	$ —	$ 82,013	$ —
Property and equipment received but unpaid as of period end	$ 143	$ 349	$ 1,359
Assets acquired under capital lease	$ —	$ 17	$ 389
Assets acquired through lease incentive	$ —	$ —	$ 1,612
Offering costs incurred but unpaid as of period end	$ 13	$ —	$ 1,280

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 an understanding of the non-coding regulatory region of the genome to advance new medicines to control the expression of disease-driving genes. The Company has built a proprietary platform designed to analyze this unexploited region of DNA in human disease tissue to identify and drug novel targets linked to genomically defined patient populations.

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.

On July 6, 2016, the Company completed an initial public offering, in which the Company issued and sold 4,600,000 shares of its common stock at a public offering price of $12.50 per share, including 600,000 shares of common stock sold pursuant to the underwriters' exercise of their option to purchase additional shares of common stock, for aggregate gross proceeds of $57.5 million (the "IPO"). The Company received approximately $49.9 million in net proceeds from the IPO after deducting $7.6 million of underwriting discounts and commissions and offering costs. Upon the closing of the IPO, all of the outstanding shares of the Company's convertible preferred stock automatically converted into 15,988,800 shares of common stock at the applicable conversion ratio then in effect. Subsequent to the closing of the IPO, there were no shares of preferred stock outstanding. In connection with the IPO, the Company amended and restated its certificate of incorporation to change the authorized capital stock to 200,000,000 shares designated as common stock, and 10,000,000 shares designated as preferred stock, all with a par value of $0.001 per share. The significant increase in common stock outstanding in July 2016 relating to the IPO and conversion of convertible preferred stock had an impact on the year-over-year comparability of the Company's net loss per share calculations throughout 2017.

On April 26, 2017, the Company issued and sold an aggregate of 2,592,591 shares of its common stock in a private placement at an offering price of $13.50 per share, for aggregate gross proceeds of $35.0 million, before deducting placement agent fees of $2.1 million and other offering expenses of $0.3 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 $54.0 million, $47.7 million and $29.8 million for the years ended December 31, 2017, 2016 and 2015, respectively. As of December 31, 2017, the Company had an accumulated deficit of $155.3 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 private placements of its preferred stock, the sale of common stock in the IPO, and a private placement of common stock in April 2017. 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 $72.0 million as of December 31, 2017, together with amounts received from Incyte Corporation ("Incyte") in connection with the Company's collaboration and option agreement with Incyte executed in January 2018 and the net proceeds from the underwritten public offering of the Company's common stock and concurrent private placement of the Company's common stock to Incyte that closed in February 2018, 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 United States generally accepted accounting principles as found in the Accounting Standards Codification ("ASC") and Accounting Standards Updates ("ASU") of the Financial Accounting Standards Board ("FASB").

In connection with preparing for its IPO, the Company effected a one-for-3.75 reverse stock split of the Company's common stock. The reverse stock split became effective on June 17, 2016. The par value and authorized shares of common stock and convertible preferred stock were not adjusted as a result of the reverse stock split. All share and per share amounts in the financial statements and notes thereto have been retroactively adjusted for all periods presented to give effect to this reverse stock split, including reclassifying an amount equal to the reduction in par value of common stock to additional paid-in capital. The financial statements have also been retroactively adjusted to reflect adjustments to the conversion price for each series of convertible preferred stock effected in connection with the reverse stock split.

Principles of Consolidation

The accompanying consolidated financial statements include the accounts of Syros Pharmaceuticals, Inc. and its wholly owned subsidiary, Syros Securities Corporation, which is a Massachusetts subsidiary formed by the Company in December 2014 to exclusively engage in buying, selling and holding securities on its own behalf. All intercompany transactions and balances have been eliminated.

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, including estimating the fair value of the Company's common stock prior to the completion of the IPO, 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.

Marketable Securities

The Company determines the appropriate classification of its marketable securities, which consist primarily of debt securities, at the time of purchase and reevaluates such designation at each balance sheet date. All of the Company's marketable securities are considered available-for-sale and carried at estimated fair values and reported in short-term marketable securities. Unrealized gains and losses on available-for-sale securities are excluded from net income and reported in accumulated other comprehensive income (loss) as a separate component of stockholders' equity (deficit). Other income, net, includes interest, dividends, amortization of premiums and discounts, realized gains and losses on sales of securities and other-than-temporary declines in the fair value of securities, if any. The cost of securities sold is based on the specific identification method. The Company regularly reviews all of its investments for other-than-temporary declines in fair value. The Company's review includes the consideration of the cause of the impairment, including the creditworthiness of the security issuers, the number of securities in an unrealized loss position, the severity and duration of the unrealized losses, whether the Company has the intent to sell the securities and whether it is more likely than not that it will be required to sell the securities before the recovery of their amortized cost basis. If the Company were to determine that the decline in fair value of an investment is below its accounting basis and the decline is other-than-temporary, the Company would reduce the carrying value of the security and record a loss for the amount of such decline.

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 Topic 820, *Fair Value Measurement* ("ASC 820"), establishes a fair value hierarchy for instruments measured at fair value that distinguished 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, and are developed based on the best information available in 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 balance sheets for cash and cash equivalents, prepaid expenses, other current assets, accounts payable and accrued expenses approximate their 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 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 research equipment 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, 2017.

Other Long-Term Assets

At December 31, 2017, other long-term assets consisted of deferred issuance costs, which included direct and incremental legal and accounting fees related to the shelf registration filed in July 2017, as well as advanced payments made to the contract research organization responsible for conducting the Company's clinical trial of SY-1425 and SY-1365. At December 31, 2016, other long-term assets primarily consisted of advanced payments made to the contract research organization responsible for conducting the Company's clinical trial of SY-1425.

Revenue Recognition

To date, the Company's only source of revenue has been a research agreement with a multinational pharmaceutical company, which expired on March 31, 2017 in accordance with its terms..

The Company recognizes revenue in accordance with ASC Topic 605, *Revenue Recognition* ("ASC 605"). Accordingly, revenue is recognized when all of the following criteria are met:

- persuasive evidence of an arrangement exists;
- delivery has occurred or services have been rendered;
- the seller's price to the buyer is fixed or determinable; and
- collectability is reasonably assured.

Amounts received prior to satisfying the revenue recognition criteria are recognized as deferred revenue in the Company's consolidated balance sheets. Amounts expected to be recognized as revenue within the 12 months following the balance sheet date are classified in current liabilities. Amounts not expected to be recognized as revenue within the 12 months following the balance sheet date are classified as deferred revenue, net of current portion.

The Company analyzes 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 evaluates 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 involves subjective determinations and requires management to make judgements about the individual deliverables and whether such deliverables are separate from other aspects of the contractual relationship. Deliverables are considered separate units of accounting provided that: (i) the delivered item(s) has value to the customer on a standalone basis and (ii) if the arrangement includes a general right of return relative to the delivered item(s), delivery or performance of the undelivered item(s) is considered probable and substantially within control of the Company. The Company's research agreement contained a single unit of accounting.

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

The Company recognized revenue under its research agreement based upon the completed performance method of revenue recognition as it was unable to reasonably estimate the period of performance of the services and the delivery of the final study report was significant to the arrangement.

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 the Company's 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 and depreciation.

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 the future 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 Topic 718, *Compensation—Stock Compensation* ("ASC 718"). ASC 718 requires all stock-based payments to employees and directors, including grants of restricted stock and stock options, to be recognized as expense in the consolidated statements of operations based on their grant date fair values. Grants of restricted stock and stock options to other service providers, referred to as non-employees, are 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 options granted using the Black-Scholes option-pricing model. Prior to June 30, 2016, the Company was a private company and as such lacks Company-specific historical and implied volatility information. Therefore, it 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. The expected term of stock options granted to non-employees is equal to the contractual term of the option award. 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.

Additionally, in March 2016, the FASB issued ASU No. 2016-09, *Compensation—Stock Compensation (Topic 718): Improvements to Employee Share-Based Payment Accounting* ("ASU 2016-09"). ASU 2016-09 simplifies several aspects of the accounting for share-based payment transactions, including the income tax consequences, classification of awards as either equity or liabilities, and an option to recognize gross stock-based compensation expense with actual forfeitures as they occur, as well as certain classification on the statement of cash flows. For public entities, ASU 2016-09 is effective for fiscal years beginning after December 15, 2016, and interim periods within those fiscal years. The Company has adopted ASU 2016-09 as of January 1, 2017. The Company has applied ASU 2016-09 using a modified retrospective approach and has adopted the option to recognize stock compensation expense with actual forfeitures recognized as they occur. The adoption of this standard had an immaterial impact to the Company's financial statements. The adoption of ASU 2016-09 also requires all excess tax benefit on stock options to be recorded in the consolidated statements of operations. The adoption did not have a material impact since the expected increase in net deferred tax assets is fully offset by a corresponding increase in the deferred tax asset valuation allowance. The amount of deferred tax assets that had not been previously recognized due to the recognition of excess tax benefits upon adoption was $0.4 million.

The Company expenses the fair value of its stock-based awards to employees on a straight-line basis over the associated service period, which is generally the vesting period. As a result of the adoption of ASU 2016-09, effective January 1, 2017, the Company accounts for forfeitures as they occur instead of estimating forfeitures at the time of grant and revising those estimates in subsequent periods if actual forfeitures differ from its estimates. Ultimately, the actual expense recognized over the vesting period will be for only those options that vest.For stock-based awards granted to consultants and non-employees, compensation expense is recognized over the period during which services are rendered by such consultants and non-employees until completed. At the end of each financial reporting period prior to completion of the service, the fair value of these awards is remeasured using the then-current fair value of such awards.

For stock-based awards that contain performance-based milestones, the Company records 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 the Company's 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.

Income Taxes

The Company accounts for income taxes in accordance with ASC Topic 740, *Income Taxes* (''ASC 740''). The Company recognizes deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the Company's financial statements or tax returns. Under this method, deferred tax assets and liabilities are determined based on differences between the financial statement carrying amounts and the tax bases of the assets and liabilities using the enacted tax rates in effect in the years in which the differences are expected to reverse. A valuation allowance against deferred tax assets is recorded if, based on the weight of the available evidence, it is more likely than not that some or all of the deferred tax assets will not be realized.

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 loss per share applicable to common stockholders is calculated by dividing net loss applicable to common stockholders by the weighted average shares outstanding during the period, without consideration for common stock equivalents. Diluted net loss 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 dilutive net loss per share applicable to common stockholders calculation, convertible preferred stock, stock options, and unvested restricted stock 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,		
	2017	2016	2015
Convertible preferred stock	—	—	12,598,370
Stock options	2,846,668	2,543,435	2,226,698
Unvested restricted stock	—	4,885	256,881
	2,846,668	2,548,320	15,081,949

The weighted average number of common shares used in net loss per share applicable to common stockholders on a basic and diluted basis were 25,406,845, 12,696,414 and 1,980,286 for the years ended December 31, 2017, 2016 and 2015, respectively.

Recent Accounting Pronouncements

In May 2014, the FASB issued ASU No. 2014-09, *Revenue From Contracts With Customers* ("ASU 2014-09"). ASU 2014-09 amends ASC 605, *Revenue Recognition*, by outlining a single comprehensive model for entities to use in accounting for revenue arising from contracts with customers. ASU 2014-09 will be effective for the Company for interim and annual periods beginning after December 15, 2017. Entities have the option of using either a full retrospective or a modified retrospective approach to adopt this new guidance. The FASB issued supplemental adoption guidance and clarification to ASU 2014-09 in March 2016, April 2016, May 2016, and December 2016 within ASU 2016-08 "Revenue from Contracts with Customers: Principal vs. Agent Considerations," ASU 2016-10 "Revenue from Contracts with Customers: Identifying Performance Obligations and Licensing," ASU 2016-12 "Revenue from Contracts with Customers: Narrow-Scope Improvements and Practical Expedients," and ASU 2016-20 "Technical Corrections and

Improvements to Topic 606, Revenue from Contracts with Customers," respectively. As of December 31, 2017, the Company had one revenue arrangement, which was completed on March 31, 2017, prior to adoption. The Company plans to use the modified retrospective approach in adopting this standard.

As described further in Note 14 – Subsequent Events, the Company entered into a target discovery, research collaboration and option agreement with Incyte in January 2018 under which the Company will use its gene control platform to identify novel therapeutic targets with a focus on myeloproliferative neoplasms, and Incyte will receive 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. Upon execution of the 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 Company is eligible to receive target selection milestone payments and option exercise fees of up to an aggregate of $54.0 million, and if products arising from the collaboration are approved, the Company would become eligible to receive from Incyte, for each validated target, a total of up to $50.0 million in development and regulatory milestone payments and up to $65.0 million in commercial milestone payments. No revenue was recognized under this agreement during the year ended December 31, 2017. The Company will recognize revenue related to this agreement using the new standard during 2018.

In February 2016, the FASB issued ASU No. 2016-02, *Leases* ("ASU 2016-02"), which applies to all leases and will require lessees to put most leases on the balance sheet, but recognize expense in a manner similar to the current standard. ASU 2016-02 is effective for fiscal years beginning after December 15, 2018 and interim periods within those years, and, as such, will be effective for the year ended December 31, 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 Company is evaluating the new guidance and the expected effect on the Company's consolidated financial statements. However, the Company anticipates recognition of additional assets and corresponding liabilities related to its operating leases. To date, the Company has one operating lease for its office and laboratory space in Cambridge, Massachusetts (Note 9).

In August 2016, the FASB issued ASU No. 2016-15, *Statement of Cash Flows (Topic 230)* ("ASU No. 2016-15"), which simplifies certain elements of cash flow classification. The new guidance is intended to reduce diversity of practice in how certain transactions are classified in the statement of cash flows. ASU No. 2016-15 is effective for annual periods beginning after December 15, 2017. The Company is currently evaluating the impact the adoption of ASU No. 2016-15 will have on its consolidated financial statements.

In November 2016, the FASB issued ASU No. 2016-18, *Restricted Cash* ("ASU No. 2016-18"). The amendments in ASU No. 2016-18 require an entity to reconcile and explain the period-over-period change in total cash, cash equivalents and restricted cash within its statements of cash flows. ASU No. 2016-18 is effective for fiscal years (including interim reporting periods within those years) beginning after December 15, 2017. Early adoption is permitted. A reporting entity must apply the amendments in ASU No. 2016-18 using a full retrospective approach. The Company believes that the adoption of this guidance will not have a significant impact on its consolidated financial statements and related disclosures.

In January 2017, the FASB issued ASU No. 2017-01, *Business Combinations (Topic 805): Clarifying the Definition of a Business* ("ASU No. 2017-01"). The amended guidance clarifies the definition of a business with the objective of adding guidance to assist entities with evaluating whether transactions should be accounted for as acquisitions (or disposals) of assets or businesses. The new accounting guidance is effective for annual periods beginning after December 15, 2017, including interim periods within those periods. Early adoption is permitted. The Company will evaluate the impact that the adoption of ASU No. 2017-01 will have on future transactions.

3. 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 income (loss). Premiums or discounts from par value are amortized to investment income over the life of the underlying security.

Cash equivalents and marketable securities, available-for-sale, consisted of the following at December 31, 2017 and December 31, 2016 (in thousands):

December 31, 2017	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
Cash Equivalents:				
Money market funds	$ 17,205	$ —	$ —	$ 17,205
Overnight repurchase agreements	15,000	—	—	15,000
Marketable Securities:				
U.S. treasury obligations	39,886	—	(42)	39,844
Total:	$ 72,091	$ —	$ (42)	$ 72,049

December 31, 2016	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
Cash Equivalents:				
Money market funds	$ 58,588	$ —	$ —	$ 58,588
Marketable Securities:				
U.S. treasury obligations	25,014	—	(9)	25,005
Total:	$ 83,602	$ —	$ (9)	$ 83,593

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 year ended December 31, 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.

At December 31, 2017, the Company held 17 securities that were in an unrealized loss position. The aggregate fair value of securities held by the Company in an unrealized loss position for less than twelve months as of December 31, 2017 was $39.8 million and there were no securities held by the Company in an unrealized loss position for more than twelve months. The Company has the intent and ability to hold such securities until recovery. The Company determined that there was no material change in the credit risk of the above marketable securities. As a result, the Company determined it did not hold any marketable securities with an other-than temporary impairment as of December 31, 2017.

4. Fair Value Measurements

Assets measured at fair value on a recurring basis are as follows (in thousands):

Description	December 31, 2017	Active Markets (Level 1)	Observable Inputs (Level 2)	Unobservable Inputs (Level 3)
Cash equivalents:				
Money market funds	$ 17,205	$ 17,205	$ —	$ —
Overnight repurchase agreements	15,000	—	15,000	—
Marketable securities:				
U.S. treasury obligations	39,844	39,844	—	—
	$ 72,049	$ 57,049	$ 15,000	$ —

Description	December 31, 2016	Active Markets (Level 1)	Observable Inputs (Level 2)	Unobservable Inputs (Level 3)
Cash equivalents:				
Money market funds	$ 58,588	$ 58,588	$ —	$ —
Marketable securities:				
U.S. treasury obligations	25,005	25,005	—	—
	$ 83,593	$ 83,593	$ —	$ —

5. Restricted Cash

At December 31, 2017 and December 31, 2016, the Company had $0.5 million in restricted cash that serves as the security deposit on the lease of the Company's current facility in Cambridge, Massachusetts. At December 31, 2017, approximately $0.2 million of the restricted cash was classified as current as it is expected to be refunded to the Company under the terms of the lease agreement.

6. Property and Equipment

Property and Equipment consists of the following (in thousands):

	Estimated useful life (in years)	December 31, 2017	December 31, 2016
Laboratory equipment	5	$ 3,978	$ 3,612
Computer equipment	3	651	401
Furniture and fixtures	4	396	395
Leasehold improvements	Shorter of 7 years or life of lease	2,613	2,599
Construction in process		—	18
		$ 7,638	$ 7,025
Less: Accumulated depreciation		(3,700)	(2,175)
Total property and equipment, net		$ 3,938	$ 4,850

Depreciation expense, including depreciation expense for assets recorded under capital leases, for the years ended December 31, 2017, 2016 and 2015 was $1.5 million, $1.3 million and $0.6 million, respectively. Laboratory equipment included assets recorded under capital leases of $0.4 million at December 31, 2017 (Note 8). Accumulated depreciation from assets recorded under capital leases was $0.2 million at December 31, 2017.

7. Accrued Expenses

Accrued expenses consist of the following (in thousands):

	December 31, 2017	December 31, 2016
External research and preclinical development	$ 5,875	$ 3,290
Employee compensation and benefits	2,494	1,911
Professional fees	1,225	819
Facilities	134	90
Restricted stock liability	—	5
	$ 9,728	$ 6,115

8. Indebtedness

Equipment Financing

In March 2015, the Company entered into a lease agreement with a vendor for certain laboratory equipment. The Company financed $0.4 million of the amount owed under the lease agreement and is required to make consecutive monthly payments of principal, plus accrued interest at 6.44%, over 36 months through March 2018. During the year ended December 31, 2017, the Company made payments of $0.2 million, of which $9,000 related to interest. At December 31, 2017, $0.1 million of principal was outstanding with respect to the equipment financing arrangement.

The following table sets forth the Company's future minimum payments due under capital leases as of December 31, 2017:

Year	(in thousands)
2018	$ 48
2019	5
2020	2
	$ 55

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 Company has an option to extend the lease for five additional years. The 2015 Lease has escalating rent payments and the Company records rent expense on a straight-line basis over the term of the lease, including any rent-free periods. The Company recorded rent expense of $0.9 million, $0.9 million, and $0.3 million for the years ended December 31, 2017, 2016 and 2015, respectively, related to the 2015 Lease. The 2015 Lease agreement required the Company to issue an original letter of credit in the amount of $0.5 million, which is included in restricted cash in the accompanying balance sheet at December 31, 2017 and December 31, 2016. At December 31, 2017, approximately $0.2 million of the restricted cash was classified as current as it is expected to be refunded to the Company under the terms of the lease agreement.

The 2015 Lease includes certain lease incentives in the form of tenant allowances. The Company has capitalized the 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 will amortize these incentives as a reduction of rent expense over the lease term. The related fixed assets will be amortized over the lease term.

The following table sets forth the Company's future minimum payments due under operating leases as of December 31, 2017:

Year	(in thousands)
2018	$ 1,288
2019	1,325
2020	1,130
	$ 3,743

License Agreements

Dana-Farber Cancer Institute, Inc. and Whitehead Institute for Biomedical Research

In February 2013, the Company entered into a license agreement with Dana-Farber Cancer Institute, Inc. ("Dana-Farber") pursuant to which the Company was granted an exclusive worldwide, sublicensable license under specified patents relating to CDK7 inhibitors and *JNK* inhibitors owned or controlled by Dana-Farber. Payments totaling $3.4 million are due to Dana-Farber if and when the Company achieves certain clinical and regulatory milestones for any licensed product, none of which have been achieved as of December 31, 2017. No future potential milestone payments have been accrued as of December 31, 2017 or December 31, 2016, respectively, as no milestones have been achieved and the agreement can be cancelled at the Company's option. Therefore, the Company had no obligation to pay any of these amounts. The Company is obligated to pay a tiered royalty on net sales for licensed products in any country subject to the license. Royalty payments, if any, would continue for the duration of the licensed patents.

In April 2013, the Company entered into a license agreement with the Whitehead Institute for Biomedical Research ("Whitehead") and Dana-Farber, pursuant to which the Company was granted a worldwide, sublicensable license under specified patents relating to *MYC* modulators owned or controlled by Whitehead and Dana-Farber.

In April 2013, the Company entered into an additional license agreement with Whitehead, pursuant to which the Company was granted a worldwide license under specified patents relating to super-enhancers owned or controlled by Whitehead.

In connection with the Whitehead agreements, the Company issued 171,674 shares of its common stock to Whitehead in April 2013. Payments totaling $3.6 million are due under the Whitehead agreements when the Company achieves certain milestones. The future potential milestone payments due under the Whitehead agreements have not been accrued as of December 31, 2017 and December 31, 2016, respectively, as no milestones have been achieved and the agreement can be cancelled at the Company's option. Therefore, the Company had no obligation to pay any of these amounts. The Company paid Whitehead and the Whitehead Institute for Genome Technology Core $0.9 million and $1.0 million during the years ended December 31, 2017 and 2016, respectively, for annual license maintenance fees and research services. Additionally, at December 31, 2017, the Company had $0.2 million in accounts payable and accrued expenses due to Whitehead and the Whitehead Institute for Genome Technology Core for research services performed during 2017.

TMRC Co. Ltd.

In September 2015, the Company entered into an exclusive license agreement with the Japanese oncology company 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. The Company made payments of $0.4 million under this supply management agreement during the year ended December 31, 2017. No payments were made under this supply management agreement during the year ended December 31, 2016.

Litigation

The Company is not party to any litigation and does not have contingency reserves established for any litigation liabilities as of December 31, 2017 or December 31, 2016.

10. 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 and approved by the stockholders on June 17, 2016, and became effective on July 6, 2016 upon the closing of the 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, nonstatutory 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 will automatically increase on January 1 of each calendar year, commencing on January 1, 2017 and ending on December 31, 2025, 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 compensation committee of 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, 2017, the number of shares reserved for issuance under the 2016 Plan was increased by 935,430 shares. At December 31, 2017, 2,880,493 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.

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 are exercisable from the date of grant for a period of ten years. The Company may grant performance-based stock option awards for which vesting accelerates upon the achievement of performance-based milestones. For certain of such awards, notwithstanding any vesting in accordance with the achievement of performance-based milestones, such awards may vest in full on the sixth anniversary of the vesting commencement date.

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 and 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 will automatically increase on the first day of each fiscal year, commencing on January 1, 2017 and ending on December 31, 2025, 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, 2017, the number of shares reserved for issuance under the 2016 ESPP was increased by 233,857 shares. At December 31, 2017, 820,523 shares remained available for future issuance under the 2016 ESPP.

Stock Options

Performance-Based Stock Options

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 preclinical and 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 year ended December 31, 2016, the Company recorded additional stock-based compensation expense of $0.2 million related to the achievement of certain performance-based milestones. The Company did not record any additional stock-based compensation expense related to the achievement of performance-based milestones for the year ended December 31, 2017. As of December 31, 2017, there was $1.0 million of unrecognized stock-based compensation expense related to the performance-based stock options granted to management, with an expected recognition period of 3.2 years.

During the year ended December 31, 2016, the Company granted options to purchase 75,000 shares of common stock to an advisor for which the vesting accelerates upon the achievement of performance-based criteria. As of December 31, 2017, no such performance-based criteria were achieved. As of December 31, 2017, there was $0.6 million of unrecognized stock-based compensation expense related to the performance-based stock options granted to management, with an expected recognition period of 8.7 years.

A summary of the status of stock options as of December 31, 2017 and December 31, 2016 and changes during the year ended December 31, 2017 is presented below:

	Shares	Weighted Average Exercise Price	Remaining Contractual Life (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding at December 31, 2016 . . .	2,543,435	$ 6.44	8.3	$ 14,898
Granted	1,368,000	11.87		
Exercised	(445,012)	4.03		
Cancelled	(619,755)	7.22		
Outstanding at December 31, 2017 . . .	2,846,668	$ 9.25	8.2	$ 5,713
Exercisable at December 31, 2017	858,927	$ 6.06	7.0	$ 3,827
Vested and expected to vest at December 31, 2017	2,846,668	$ 9.25	8.2	$ 5,713

The intrinsic value of options exercised during the years ended December 31, 2017, 2016 and 2015 was $4.6 million, $2.4 million, and $2.0 million, respectively.

Cash received from option exercises during the years ended December 31, 2017, 2016, and 2015 was $1.8 million, $0.4 million, and $0.4 million, respectively.

Restricted Common Stock

From time to time, upon approval by the Company's board of directors, certain employees and advisors have been granted restricted shares of common stock with time- and performance-based vesting criteria. These shares of restricted stock are subject to repurchase rights. Accordingly, the Company has recorded the proceeds from the issuance of restricted stock as a liability in the consolidated balance sheets included as a component of accrued expenses or other long term liabilities based on the scheduled vesting dates. The restricted stock liability is reclassified into stockholders' equity (deficit) as the restricted stock vests over time or upon the achievement of performance.

A summary of the status of unvested restricted common stock as of December 31, 2017 and December 31, 2016 and changes during the year ended December 31, 2017 is presented below:

	Shares	Weighted Average Grant Date Fair Value
Unvested at December 31, 2016	4,885	$ 0.98
Vested	(4,885)	0.98
Repurchased	—	—
Unvested at December 31, 2017	—	$ —

The total fair value of restricted stock vested during the years ended December 31, 2017, 2016, and 2015 was $1,000, $0.1 million, and $0.1 million, respectively, based upon the number of restricted stock awards vested multiplied by the fair value of the Company's common stock on the grant date.

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,		
	2017	2016	2015
Weighted-average risk-free interest rate	2.07 %	1.36 %	1.78 %
Expected dividend yield	— %	— %	— %
Expected option term	6.05	5.98	6.09
Volatility	87.83 %	85.39 %	82.71 %

The weighted‑average grant date fair value per share of options granted in the years ended December 31, 2017, 2016 and 2015 was $8.75, $8.58 and $4.88, respectively.

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

	Year Ended December 31,		
	2017	2016	2015
Research and development	$ 1,666	$ 2,980	$ 2,733
General and administrative	2,753	1,254	500
Total stock-based compensation expense	$ 4,419	$ 4,234	$ 3,233

As of December 31, 2017, there was $11.9 million of total unrecognized compensation cost related to non-vested stock options granted to employees, which is expected to be recognized over a weighted-average period of 2.9 years. Additionally, as of December 31, 2017, there was $0.1 million of total unrecognized compensation cost related to non-vested stock options granted to non-employees, excluding those subject to performance-based criteria described above. 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.

11. 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, 2017 and 2016 are as follows:

	Year Ended December 31,	
	2017	2016
Current	$ 7	$ 2
Deferred	—	—
Total	$ 7	$ 2

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, 2017, 2016 and 2015:

	Year ended December 31,		
	2017	2016	2015
Federal income tax computed at federal statutory tax rate	34.00 %	34.00 %	34.00 %
State income tax, net of federal benefit	5.35	4.79	4.70
Permanent items	(1.57)	(2.83)	(3.33)
Federal and state research and development credits	7.36	2.93	2.66
Rate change	(31.79)	—	—
Other	0.66	(0.08)	0.12
Change in valuation allowance	(14.02)	(38.81)	(38.15)
Effective income tax rate	(0.01)%	0.00 %	0.00 %

On December 22, 2017, H.R.1., formerly known as the Tax Cuts and Jobs Act, was signed into law. The new law did not have a significant impact on the Company's consolidated financial statements for the year ended December 31, 2017 because it maintains a valuation allowance on the majority of its net operating losses and other deferred tax assets. However, the reduction of the U.S. federal corporate tax rate from 35% to 21% resulted in increases to the amounts reflected in the effective tax rate attributable to "change in valuation allowance" and "rate change" in the Company's effective tax rate reconciliation table above for the year ended December 31, 2017 compared to the years ended December 31, 2016 and 2015. The change in the U.S. federal corporate tax rate, which is effective January 1, 2018, is also reflected in the Company's deferred tax table below. Lastly, the Company has discussed the possible impact of Staff Accounting Bulletin No. 118 ("SAB 118") on the Company's consolidated financial statements below.

The principal components of the Company's deferred tax assets and liabilities consist of the following at December 31, 2017 and 2016 (in thousands):

	Year ended December 31,	
	2017	2016
Deferred tax assets:		
Federal and state net operating loss carryforwards	$ 37,411	$ 33,846
Tax credit carryforwards	7,573	3,350
Intangible assets	56	197
Stock-based compensation	1,059	247
Leasehold incentive	240	467
Other	1,237	1,605
Total deferred tax assets	47,576	39,712
Less valuation allowance	(47,576)	(39,624)
Net deferred tax assets	—	88
Deferred tax liabilities:		
Fixed assets	—	(88)
Total deferred tax liabilities	—	(88)
Net deferred taxes	$ —	$ —

As of December 31, 2017 the Company had federal net operating loss ("NOL") carryforwards of approximately $136.4 million and state net operating loss carryforwards of $138.8 million which are available to reduce future taxable income. The Company also had federal tax credits of approximately $6.1 million and state tax credits of $1.8 million which may be used to offset future tax liabilities. The NOL and tax credit carryforwards will expire at various dates through 2037. 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, 2017 and 2018, 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 $8.0 million in 2017 and $18.5 million in 2016 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, 2017 and 2016 the Company had no unrecognized tax benefits. The Company's policy is to recognize both interest and penalties related to unrecognized tax benefits in income tax expense.

The federal and state income tax returns are generally subject to examinations for the tax years ended December 31, 2014 through December 31, 2017. 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.

On December 22, 2017, the SEC staff issued SAB 118 to address the application of GAAP in situations when a registrant does not have the necessary information available, prepared, or analyzed (including computations) in reasonable detail to complete the accounting for certain income tax effects of H.R.1. The Company has recognized the provisional tax impacts related the revaluation of deferred tax assets and liabilities and included these amounts in its financial statements for the year ended December 31, 2017. The ultimate impact may differ from these provisional amounts, possibly materially, due to, among other things, additional analysis, changes in interpretations and assumptions the Company has made, additional regulatory guidance that may be issued, and actions the Company may take as a result of H.R.1. The Company's accounting treatment is expected to be complete when the 2017 U.S. corporate income tax return is filed in 2018.

12. Research Agreement

In November 2014, the Company entered into a research agreement with a multinational pharmaceutical company (the "Counterparty") for purposes of mapping immune cell super-enhancers ("SE") and transcriptional targets in autoimmune disease. Under the research agreement, the Company is responsible for the conduct of all activities under separate projects, as defined in the research agreement, associated with generating SE and transcriptional maps of the cell/tissue supplied by the Counterparty. Upon the completion of each project, the Counterparty determined whether to commence the next project under the research agreement upon written notification.

The research agreement was amended in November 2016 to extend the term to March 31, 2017. The research agreement terminated automatically on March 31, 2017 in accordance with its terms.

The Company recognized revenue on a completed performance basis for each project performed under the agreement, as the Company does not have the ability to reasonably estimate the period of performance and the final study report for each project is significant to the overall arrangement. The Company recognized revenue of $1.1 million and $0.3 million during the years ended December 31, 2017 and December 31, 2016, respectively, under the agreement.

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 basis. Company contributions to the plan may be made at the discretion of the board of directors. Effective September 1, 2017, the Company instituted an employer match of 100% of the amount you contribute to the Plan for each payroll period up to the first 1% of Plan Compensation plus 50% of the amount you contribute between 1% and 6% of Plan Compensation. For the year ended December 31, 2017, the Company contributed $0.3 million to the 401(k) Plan.

14. Subsequent Events

Collaboration Agreement

On January 8, 2018, the Company and Incyte Corporation entered into a Target Discovery, Research Collaboration and Option Agreement (the "Collaboration Agreement"). Under the Collaboration Agreement, the Company will use its proprietary gene control platform to identify novel therapeutic targets with a focus on myeloproliferative neoplasms, and Incyte will receive 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. Incyte will have exclusive worldwide rights to develop and commercialize any therapies under the collaboration that modulate those validated targets.

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 Company's activities under the Collaboration Agreement are subject to a joint research plan and, subject to certain exceptions, Incyte will be responsible for funding the Company's activities under the research plan, including amounts in excess of the pre-paid research funding amount. The Company is obligated to make a payment to Whitehead representing a percentage of the up-front cash consideration received under the Collaboration Agreement.

The Company will be 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 option 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, the Company will be eligible to receive milestone payments and, if approved and commercialized, royalty payments from Incyte. For each of the seven validated targets, the Company 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, the Company 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, the Company would become eligible to receive low single-digit royalties on net sales of such product.

The term of Collaboration Agreement began on January 8, 2018 and, unless terminated by a party early, will continue until all royalty obligations for products arising from the collaboration expire. The Collaboration Agreement may be terminated by Incyte for convenience on sixty (60) days' prior written notice to the Company, or by the Company 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 the Company. The Collaboration 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 Collaboration Agreement by the other party or immediately in the case of certain bankruptcy events. 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 Collaboration Agreement in its entirety or, as applicable, in relation to the relevant validated target and associated therapeutic products.

Following entry into the Collaboration Agreement, the Company's Board of Directors accelerated the vesting of 63,793 shares underlying performance-based stock options granted to members of the Company's management team.

Stock Purchase Agreement

On January 8, 2018, the Company entered into a Stock Purchase Agreement with Incyte (the "SPA"), pursuant to which Incyte agreed to purchase 793,021 shares of the Company's common stock, par value $0.001 per share, for an aggregate purchase price of $10.0 million in cash, or $12.61 per share, in a private placement. The purchase price represents a thirty percent (30%) premium to the volume-weighted sale price of the shares of the Company's common stock over the fifteen (15) trading day period immediately preceding the date of the SPA. The Company is obligated to make a payment to Whitehead representing a percentage of the equity premium received under the SPA. The Shares are subject to a lock-up restriction and a market stand-off agreement for a period of 12 months following the closing of the sale of the shares (the "Closing"). Pursuant to the terms of the SPA, the Company filed a registration statement covering the resale by Incyte of the Shares on January 19, 2018.

In addition, from the Closing until the earlier of the second anniversary of the Closing or the expiration or termination of the Collaboration Agreement, the Company has granted to Incyte the right to purchase up to its pro rata share of the securities offered in certain subsequent offerings of the Company's common stock or common stock equivalents, subject to the terms and conditions set forth in the SPA.

Sale of Securities through Public Offering

On January 30, 2018, the Company issued and sold an aggregate of 4,188,481 shares of its common stock in a public offering at a price per share $9.55 per share, resulting in gross proceeds of $40.0 million before deducting underwriting commissions and fees estimated to be approximately $2.7 million. Additionally, on February 2, 2018, the underwriters exercised their option to purchase an additional 628,272 shares at a price per share of $9.55, resulting in additional gross proceeds of $6.0 million.

In addition, on February 2, 2018, we also closed a concurrent private placement of 125,656 shares of our common stock to Incyte Corporation at a price of $9.55 per share, resulting in proceeds to us of $1.2 million. The Company closed an additional private placement of 18,849 shares of its common stock to Incyte on February 7, 2018 at a price of $9.55 per share, resulting in gross proceeds to the Company of $0.2 million.

15. Selected Quarterly Financial Data (unaudited)

The following table contains selected quarterly financial information for 2017 and 2016. 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, 2017	June 30, 2017	September 30, 2017	December 31, 2017
Revenue	$ 1,101	$ —	$ —	$ —
Operating expenses:				
Research and development	9,628	10,041	10,447	11,780
General and administrative	3,086	3,472	3,593	3,740
Total operating expenses	12,714	13,513	14,040	15,520
Loss from operations	(11,613)	(13,513)	(14,040)	(15,520)
Other income, net	98	145	215	218
Net loss applicable to common stockholders	$ (11,515)	$ (13,368)	$ (13,825)	$ (15,302)
Net loss per share applicable to common stockholders - basic and diluted	$ (0.49)	$ (0.52)	$ (0.53)	$ (0.58)
Weighted-average number of common shares used in net loss per share applicable to common stockholders - basic and diluted	23,393,448	25,584,147	26,259,216	26,316,550

	Three Months Ended			
	March 31, 2016	June 30, 2016	September 30, 2016	December 31, 2016
Revenue	$ —	$ —	$ —	$ 317
Operating expenses:				
Research and development	8,265	9,525	11,584	8,443
General and administrative	2,371	2,540	2,633	2,919
Total operating expenses	10,636	12,065	14,217	11,362
Loss from operations	(10,636)	(12,065)	(14,217)	(11,045)
Other income, net	48	44	48	80
Net loss	$ (10,588)	$ (12,021)	$ (14,169)	$ (10,965)
Accrued dividends on preferred stock	(1,737)	(1,823)	(121)	—
Net loss applicable to common stockholders	$ (12,325)	$ (13,844)	$ (14,290)	$ (10,965)
Net loss per share applicable to common stockholders - basic and diluted	$ (5.15)	$ (5.42)	$ (0.65)	$ (0.47)
Weighted-average number of common shares used in net loss per share applicable to common stockholders - basic and diluted	2,394,470	2,553,146	22,012,743	23,374,734

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 officer, 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 and principal financial officer, has evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2017. Based upon such evaluation, our Chief Executive Officer and Principal Financial Officer has 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

This Annual Report on Form 10-K does not include a report of management's assessment regarding internal control over financial reporting or an attestation report of our independent registered public accounting firm due to a transition period established by rules of the SEC for newly public companies.

Changes in Internal Control Over Financial Reporting

During the year ended December 31, 2017, we implemented an accounting system for purposes of tracking and accounting for stock-based awards, as well as an enterprise resource system for the purposes of maintaining our general ledger and reporting. 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) during the year ended December 31, 2017 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

None.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required by this Item 10 will be included under the captions "Executive Officers," "Election of Directors" and "Section 16(a) Beneficial Ownership Reporting Compliance" in our definitive proxy statement to be filed with the SEC with respect to our 2018 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 2018 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 2018 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 2018 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 2018 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 113 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	8-K	7/6/16	3.1	
3.2	Amended and Restated Bylaws of the Registrant	8-K	7/6/16	3.2	
4.1	Form of common stock certificate	S-1^	6/3/16	4.1	
4.2	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	
4.3	Sales Agreement dated July 20, 2017 by and between the Registrant and Cowen and Company LLC	S-3^^	7/20/17	1.2	
4.4	Stock Purchase Agreement dated January 8, 2018 by and between the Registrant and Incyte Corporation, as amended				X
4.5	Underwriting Agreement dated January 30, 2018 by and among the Registrant, J.P. Morgan Securities LLC, Cowen and Company, LLC and Piper Jaffray and Co., as representatives of the several underwriters named thereing	8-K	1/31/18	1.1	
4.6	Securities Purchase Agreement dated April 20, 2017 by and among the Registrant and the persons party thereto	8-K	4/21/17	10.1	
4.7	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*	2016 Employee Stock Purchase Plan	S-1^	6/3/16	10.8	
Agreements with Directors and Executive Officers					
10.9*	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	
10.10*	Offer Letter dated August 25, 2015 by and between the Registrant and Kyle D. Kuvalanka, as amended	S-1^	6/3/16	10.10	
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 September 9, 2016 by and between the Registrant and Gerald E. Quirk, Esq.	10-K	3/20/17	10.12	
10.13*	Offer Letter dated November 6, 2017 by and between the Registrant and Jeremy Springhorn, Ph.D.				X
10.14*	Consulting Agreement dated August 8, 2012 by and between the Registrant and Richard A. Young, Ph.D., as amended	10-K	3/20/17	10.13	

Exhibit No.	Description	Incorporation by Reference: Form	SEC Filing Date	Exhibit Number	Filed with this 10-K
10.15*	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					
10.16+	Exclusive License Agreement dated February 22, 2013 by and between the Registrant and the Dana-Farber Cancer Institute, Inc.	S-1^	6/3/16	10.13	
10.17+	Exclusive License Agreement dated April 1, 2013 by and among the Registrant, the Whitehead Institute for Biomedical Research and the Dana-Farber Cancer Institute, Inc.	S-1^	6/3/16	10.14	
10.18+	Exclusive License Agreement dated April 4, 2013 by and between the Registrant and the Whitehead Institute for Biomedical Research	S-1^	6/3/16	10.15	
10.19+	Amended and Restated Cancer License Agreement dated April 28, 2016 by and between the Registrant and TMRC Co., Ltd.	S-1^	6/3/16	10.16	
10.20+	Supply Management Agreement dated April 28, 2016 by and between the Registrant and TMRC Co., Ltd.	S-1^	6/3/16	10.18	
10.21	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	
10.22+	Target Discovery, Research Collaboration and Option Agreement dated January 8, 2018 by and between the Registrant and Incyte Corporation				X
Leases					
10.23	Lease dated March 13, 2015 by and between the Registrant and 620 Memorial Leasehold LLC	S-1^	6/3/16	10.17	
Subsidiaries, Consents and Certifications					
21.1	Subsidiaries of the Registrant				X
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

^ 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 12, 2018

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 and Financial Officer*)	March 12, 2018
/s/ Michael Inbar Michael Inbar	Controller	March 12, 2018
/s/ Peter Wirth Peter Wirth	Chair of the Board of Directors	March 12, 2018
/s/ Srinivas Akkaraju, M.D., Ph.D. Srinivas Akkaraju, M.D., Ph.D.	Director	March 12, 2018
/s/ Marsha H. Fanucci Marsha H. Fanucci	Director	March 12, 2018
/s/ Amir Nashat, Ph.D. Amir Nashat, Ph.D.	Director	March 12, 2018
/s/ Robert T. Nelsen Robert T. Nelsen	Director	March 12, 2018
/s/ Sanj K. Patel Sanj K. Patel	Director	March 12, 2018
/s/ Vicki L Sato, Ph.D. Vicki L. Sato, Ph.D.	Director	March 12, 2018
/s/ Phillip A. Sharp, Ph.D. Phillip A. Sharp, Ph.D.	Director	March 12, 2018
/s/ Richard A. Young, Ph.D. Richard A. Young, Ph.D.	Director	March 12, 2018

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

Marsha H. Fanucci
Former Chief Financial Officer, Millennium Pharmaceuticals

Amir Nashat, Ph.D.
Managing Partner, Polaris Venture Partners

Robert T. Nelsen
Managing Director, ARCH Venture Partners

Sanj K. Patel
Chief Executive Officer and Chairman, Kiniksa Pharmaceuticals

Vicki L. Sato, Ph.D.
Former Professor of Management Practice, Harvard Business School

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

ANNUAL MEETING

The Annual Meeting of Stockholders will be held at 1:00 p.m. EDT on June 14, 2018 at:

Syros Pharmaceuticals, Inc.
620 Memorial Drive, Suite 300
Cambridge, MA 02139

INDEPENDENT AUDITORS

Ernst & Young LLP
Boston, MA

INVESTOR INQUIRIES

Hannah Deresiewicz
Stern Investor Relations, Inc.
212-362-1200
hannahd@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 hannahd@sternir.com or sending a written request to:

Investor Relations
Syros Pharmaceuticals, Inc.
620 Memorial Drive, Suite 300
Cambridge, MA 02139

www.syros.com