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, 2016
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 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	☐

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, 2016, 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 $24,325,102, based on the last reported sale price of such stock on the NASDAQ Global Market as of such date.
As of February 28, 2017, the registrant had 23,392,918 shares of Common Stock, $0.001 par value per share, outstanding.
Portions of the registrant's definitive proxy statement for its 2017 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, 2016, are incorporated by reference into Items 10, 11, 12, 13 and 14 of Part III of this Annual Report on Form 10-K.

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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 plans to seek to enter into collaborations for the development and commercialization of certain product candidates;
- 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 the understanding of the 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 disease-driving 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 and drug novel targets linked to genomically defined patient populations. 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. By focusing on genomically defined subsets of patients, we believe we can conduct efficient clinical trials with a higher likelihood of success. We are currently focused on developing treatments for cancer and immune-mediated diseases and are building a pipeline of gene control medicines.

In September 2016, we began enrolling patients in a Phase 2 clinical trial for our lead product candidate, SY-1425 (tamibarotene), an oral, potent and selective retinoic acid receptor alpha, or RARα agonist, in genomically defined subsets of patients with relapsed or refractory acute myelogenous leukemia, or AML, and relapsed high-risk myelodysplastic syndrome, or MDS. In the fourth quarter of 2016, an investigational device exemption for the assay being used to select patients for this trial was approved by the U.S. Food and Drug Administration, or FDA. With this approval, we have expanded this trial to include newly diagnosed AML patients who are at least 60 years old and are not suitable candidates for standard chemotherapy, and lower-risk, transfusion-dependent MDS patients. During 2017, we intend to further expand this trial to explore the safety and efficacy of SY-1425 when combined with azacitidine, a hypomethylating agent that is commonly used to treat AML, in newly diagnosed AML patients who are at least 60 years old and not suitable candidates for standard chemotherapy. We also plan to initiate a Phase 1 clinical trial for our development candidate SY-1365, a highly potent and selective small molecule inhibitor of cyclin-dependent kinase 7, or CDK7, in patients with advanced solid tumors in the second quarter of 2017. Both of these programs may have potential in additional disease indications. Using our platform, we are also generating a pipeline of novel preclinical drug candidates in cancer, including immuno-oncology, and advancing our research efforts in rare cancers and in autoimmune and rare genetic diseases. We plan to advance one of our four preclinical programs to support a potential investigational new drug application, or IND, filing in 2019. Our goal is to build a fully integrated biopharmaceutical company based on our leadership position in gene control.

The discovery and development of targeted therapies, in which the right drug is matched to the right patient, has dramatically improved the ability to treat certain cancers and other serious diseases. Targeted drug discovery and development to date, however, has focused almost exclusively on genetic alterations found in regions of DNA that code for proteins, which represent less than 2% of the entire genome, and the identification of new drug targets by sequencing these coding regions has been largely exhausted. Moreover, in cancer, inhibiting abnormal proteins resulting from single genetic alterations in coding DNA can often lead to drug resistance and limited durable clinical benefit. 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.

Researchers have long believed that alterations in non-coding regions of DNA, which account for the other 98% of the genome, play a key role in driving disease. Until recently, however, the scientific community lacked the tools to study these regions of the genome, rendering them poorly understood and largely unexploited for targeted drug discovery and development. The work of our scientific founders, leaders in the field of gene control, as well as other academic researchers is now shedding light on the importance of non-coding regions of the genome in maintaining health and driving disease. Rapidly growing scientific evidence points to non-coding regions of DNA as fundamental to determining cell type and function and to alterations in these non-coding regions as involved in the development and progression of a broad range of diseases.

While all cells share the same genome, each of the nearly 200 different cell types in the human body has a different function. For example, a skin cell functions differently from a muscle cell despite sharing the exact same DNA. What determines a cell's type and function is the specific set of genes that is expressed, or turned "on" or "off," in that particular cell. This coordinated activation and repression of genes, known as the cell's gene expression program, is controlled by non-coding regions of the genome. Alterations in these non-coding regions change a cell's gene expression

program, altering its normal function and leading to disease. 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.

The relatively few gene control medicines available today are among the most important targeted therapies and are widely used for their approved indications. Drugs targeting specialized proteins known as transcription factors that play a central role in the expression of disease-driving genes, such as estrogen receptors in breast cancer, androgen receptors in prostate cancer and glucocorticoid receptors in inflammation, are important examples of gene control medicines that have produced transformative patient benefits. For example, tamoxifen, a gene control medicine that targets a transcription factor, revolutionized the treatment of certain breast cancers and is prescribed 1.9 million times annually in the United States, illustrating the significant therapeutic potential of gene control medicines. However, the difficulty of studying non-coding regions of the genome has historically prevented a systematic approach to identifying these critical points of therapeutic intervention.

We are solely focused on the discovery and development of gene control medicines. Building on the discoveries of our scientific founders, 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 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 consists of two fundamental pillars: identifying novel gene control targets linked to genomically defined patient populations, and drugging gene control targets.

The first pillar of our platform is designed to systematically and efficiently home in on the specific set of genes most crucial to determining a cell's type and function. Starting from human tissue samples, we compare diseased cells to normal cells and analyze the cells of different patient subsets within a disease to identify alterations in gene expression programs that represent optimal points of therapeutic intervention and associated biomarkers for patient selection. Because our approach is based on patient tissue, it has the potential to identify targets that are undetectable in cell-based disease models, where the structure the regulatory genome has been lost through serial passage in tissue culture. We home in on a cell's gene expression program by using genomic tools to locate super-enhancers, which are highly specialized regions of non-coding DNA that are central to orchestrating gene expression programs and drive the increased expression of the genes crucial to the function of a given cell. Analysis of super-enhancers and their associated genes provides critical insights into changes in gene expression programs that contribute to disease. We have invested significant resources in our tissue processing, genomics and computational biology capabilities to industrialize the analysis of gene expression programs to reveal the genes crucial to cell type and function in diseased cells. We have amassed one of the largest known datasets of gene expression programs across a wide range of human diseases and cell types and have validated multiple novel disease targets and biomarkers. To date, we have analyzed or are in the process of analyzing gene expression programs in AML, breast cancer, ovarian cancer, hepatocellular carcinoma, pancreatic cancer, renal cell carcinoma, glioblastoma, immune cells from the tumor microenvironment, non-disease and lupus immune cells, polycystic kidney disease, spinal muscular atrophy and Alzheimer's disease. Through those efforts, we have identified novel drug targets in oncology, immuno-oncology and autoimmune 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 candidate SY-1425 as well as additional novel preclinical drug candidates in earlier stages of research and development. We plan to analyze gene expression programs in additional cancers, inflammatory disorders and rare genetic diseases. Our long-term goal is to analyze gene expression programs in all serious diseases where we believe currently underserved patients can benefit from gene control medicines.

The second pillar of our platform is our small molecule chemistry capabilities to drug gene control targets. While our platform is capable of identifying drug targets across a broad range of target classes and therapeutic modalities, our internal drug discovery effort is focused on small molecule chemistry to target specialized proteins responsible for gene expression, including transcription factors such as nuclear hormone receptors, transcriptional kinases and other transcriptional and regulatory proteins. We focus on these specialized proteins for several reasons.

First, 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. Transcription factors bind directly to DNA sequences to control the transcription of genetic information from DNA. Transcription factors perform this function with other transcriptional and regulatory proteins, including transcriptional kinases. Second, transcriptional and regulatory proteins have historically been difficult to drug and represent an opportunity to bring novel and differentiated therapies to patients. Third, we have built a differentiated combination of expertise, tools and capabilities that we believe will give us cutting-edge insights into drugging transcriptional and regulatory proteins. Through significant investments in developing our capabilities in biochemistry, structural biology and medicinal chemistry and in developing a sophisticated suite of proprietary assays, which are internally developed tests that we use to measure the biochemical, biophysical, cellular and genomic activity of known and novel compounds against gene control targets, we believe we will be able to overcome challenges that have prevented others from systematically and successfully developing gene control medicines. We are building a pipeline of product candidates to modulate gene expression programs through two distinct approaches: internal efforts to discover novel drugs against our validated gene control targets and externally focused efforts to link existing drugs to novel genomically defined patient populations identified through our platform. These externally focused efforts could enable to us identify drugs that we may seek to in-license or acquire or use as starting points for our own drug discovery and development programs to accelerate our development path. Our CDK7 inhibitor, SY-1365, demonstrates our ability to create proprietary gene control drug candidates targeting transcriptional biology. Our SY-1425 program demonstrates our ability to link existing drugs to novel genomically defined subsets of patients, with the aim of accelerating our clinical development path.

We are leveraging our platform to develop a pipeline of gene control product candidates. Our most advanced drug programs are summarized in the table below:

Program	Initial Indications	Planned Milestones	Potential Future Indications	Syros Commercial Rights
SY-1425 (RARα agonist)	AML and MDS	Continue enrolling Phase 2 clinical trial; expand trial to Europe Initiate combination dosing with azacitidine Expect initial data readout in fall 2017	Breast cancer Acute promyelocytic leukemia (APL)*	North America, Europe
SY-1365 (CDK7 inhibitor)	Advanced solid tumors, including triple-negative breast, ovarian and small cell lung cancers	Initiate Phase 1 clinical trial in 1H 2017 Expect initial data readout in 1H 2018	AML Acute lymphocytic leukemia Pediatric cancers	Worldwide

* Because we are focused on developing SY-1425 in patients with our *RARA* biomarker, we do not currently plan to develop SY-1425 in APL at this time. We may, however, do so in the future.

Our lead product candidate, SY-1425, is an oral, potent and selective agonist, or activator, of the transcription factor RARα. We are currently enrolling patients in a Phase 2 clinical trial in genomically defined subsets of relapsed or refractory AML and relapsed high-risk MDS patients. In the fourth quarter of 2016, an investigational device exemption for the assay being used to select patients for this trial was approved by the FDA. With this approval, we have expanded this trial to include newly diagnosed AML patients who are at least 60 years old and are not suitable candidates for standard chemotherapy, and lower-risk, transfusion-dependent MDS patients. During 2017, we intend to further expand this trial to explore the safety and efficacy of SY-1425 when combined with azacitidine, a hypomethylating agent that is commonly used to treat AML, in newly diagnosed AML patients who are at least 60 years old and not suitable candidates for standard chemotherapy.

Using our platform, we identified subsets of AML and breast cancer patients who have a super-enhancer associated with the *RARA* gene. We identified a proprietary biomarker, which we refer to as the *RARA* biomarker, related to the super-enhancer associated with *RARA*. The super-enhancer associated with *RARA* is believed to lock cells in an immature, proliferative and undifferentiated state. Treatment with SY-1425 in cancer cells with the super-enhancer associated with *RARA* appears to promote differentiation of these cells. In *in vivo* mouse models implanted with human AML tumors, SY-1425 was observed to be effective in stopping the growth of tumors with the *RARA* biomarker but not in tumors without the *RARA* biomarker. Importantly, a strong survival benefit was seen in mice with *RARA* biomarker-positive tumors that were treated with SY-1425. We observed the *RARA* biomarker in approximately 25% of AML tissues we analyzed. We believe that a similar percentage of AML and MDS patients will have the *RARA* biomarker. Based on our current clinical development plan, we believe that the potential market opportunity for SY-1425 is approximately 12,250 patients diagnosed annually with AML and MDS in the United States, Canada and the five largest European countries by population, Germany, the United Kingdom, France, Spain and Italy. These patient populations include relapsed or refractory AML patients, AML patients who are elderly or unfit for standard treatments, relapsed high-risk MDS patients and lower-risk transfusion-dependent MDS patients. Similarly, we have observed the *RARA* biomarker in approximately 35% of breast cancer patient samples we analyzed, leading us to believe that approximately 55,000 metastatic breast cancer patients diagnosed annually in the countries listed above could benefit from SY-1425.

We have the exclusive North American and European commercial rights to the existing preclinical data for SY-1425 in human cancer under our license agreement with TMRC Co., Ltd., or TMRC. SY-1425 is approved as tamibarotene in Japan for the treatment of acute promyelocytic leukemia, or APL, a form of AML, for which the drug has a well characterized efficacy and safety profile. Because we are focused on developing SY-1425 in patients with our *RARA* biomarker, we do not currently plan to develop SY-1425 in APL at this time. We may, however, do so in the future.

Our development candidate SY-1365 is a highly potent and selective small molecule inhibitor of the transcriptional kinase known as cyclin-dependent kinase 7, or CDK7. We are investigating SY-1365 for the treatment of cancers that are dependent on a high and constant expression of certain transcription factors for their growth and survival, a phenomenon known as transcriptional addiction, and plan to initially develop it in advanced solid tumors, including triple negative breast, ovarian and small cell lung cancers. In preclinical studies, SY-1365 induced tumor regression in xenograft models of triple negative breast cancer, which we refer to as TNBC, and AML. We have completed IND-enabling activities for SY-1365 and plan to initiate a Phase 1 clinical trial in patients with advanced solid tumors in the second quarter of 2017. We have chosen to enroll patients with advanced solid tumors in our first clinical trial based on the high levels of efficacy observed in preclinical studies, the high degree of transcriptional dysregulation in TNBC and other select solid tumors and the significant unmet medical need of these patients. Subject to strong clinical results, we believe there could be an opportunity for accelerated clinical development.

We currently have four programs in our early preclinical pipeline, including programs directed to the development of a CDK7 inhibitor that can be administered orally, inhibitors of cyclin-dependent kinase 12/13, and two other programs in the fields of cancer and immuno-oncology. We plan to advance at least one of these preclinical programs to support a potential Investigational New Drug application, or IND, filing in 2019, consistent with our objective of filing, on average, an IND every other year. We also intend to apply our platform to identify novel targets in rare cancers and genetic diseases.

We were founded by leaders in the field of gene control from the Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology, or Whitehead, and the Dana-Farber Cancer Institute, or Dana-Farber, an affiliate of Harvard Medical School. Many of our employees have been members of teams that uncovered innovative scientific findings and delivered highly impactful drugs to the marketplace. Our management team consists of drug discovery, development and commercialization experts with experience in translating scientific discoveries into innovative treatments, including Avonex and Tysabri for multiple sclerosis, Velcade and Ninlaro for hematological malignancies, Ibrance for breast cancer, Entyvio for ulcerative colitis and Kalydeco and Orkambi for cystic fibrosis.

Our Strategy

Our mission is to transform the lives of patients through the creation of novel gene control medicines by building a fully integrated, leading biopharmaceutical company. To achieve this mission, we are executing on the following strategy:

- **Rapidly and efficiently advance our lead programs through clinical development.** In the three years since we established our platform, we advanced SY-1425 into a Phase 2 clinical trial in genomically defined subsets of relapsed or refractory AML and relapsed high-risk MDS patients and expect to initiate a Phase 1 clinical trial of SY-1365 in patients with advanced solid tumors in the second quarter of 2017. For both of these programs, we intend to enrich our clinical trials with patients most likely to respond, which we believe will enable us to rapidly and efficiently establish clinical proof-of-concept. Because AML, MDS and transcriptionally-addicted solid tumors represent diseases with significant unmet medical need, we could be eligible, subject to encouraging clinical results, to apply for Breakthrough Therapy designation and Fast Track designation which, if granted, could accelerate clinical development and regulatory review.

- **Develop a robust pipeline of gene control product candidates.** We plan to continue leveraging our gene control platform to systematically and efficiently pinpoint genes that cause disease and to identify optimal therapeutic points of intervention in genomically defined patient populations. Employing our pioneering drug discovery and development approach, we intend to continue to either internally create selective small molecule drugs against these targets or link existing drugs to novel patient populations, enabling us to potentially accelerate our clinical development path. We aim to generate at least one IND submission every other year, on average.

- **Maintain our leadership position in the field of gene control.** We are pioneering a novel approach to discover and develop gene control medicines. To fortify our leadership position, we intend to enhance our technologies to create the most extensive dataset of gene expression programs. We also intend to expand our validation technologies to continue to identify and validate novel targets and biomarkers across many serious diseases. Our long-term goal is to analyze gene expression programs in serious diseases where gene control is a potential viable therapeutic strategy and to identify and drug novel targets based on our understanding of these gene expression programs. We plan to continue investing in building our drugging capabilities, including developing additional proprietary assays and enhancing our biochemistry, structural biology and medicinal chemistry expertise to create or acquire gene control medicines targeting disease drivers identified by our platform.

- **Continue to foster a culture of innovation.** We are committed to pioneering science and to leadership in gene control medicines. Our employees are critical to the successful achievement of our leadership vision. We will continue to foster an environment that encourages innovation, excellence and productivity and develops our team as leaders in the field of gene control.

- **Execute strategic collaborations to maximize value and extend the potential of our gene control platform across multiple disease areas.** We intend to engage in strategic collaborations around both our programs and our platform. With respect to our programs, we currently have the exclusive right to develop and commercialize SY-1425 in North America and Europe for all cancer indications. We currently retain full commercial rights to SY-1365 and all our other preclinical programs. We intend to maintain U.S. commercial rights for these programs, while pursuing collaborations that could maximize value for these programs by allowing us to expand our geographic reach and expand into additional indications. With respect to our platform, we are seeking target and drug discovery collaborations that allow us to expand the potential of our platform in additional cancers and other serious diseases beyond those that we can address on our own. We believe that our platform provides significant optionality for collaborations around drug modalities and target classes that fall outside of our current focus on small molecule drugs targeting transcriptional and regulatory proteins.

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 by non-coding regions of the genome. The process of gene expression is carried out by a number of cellular components, key to which are transcription factors, transcriptional kinases and other transcriptional and regulatory proteins. These transcriptional and regulatory proteins bind with specific regions of non-coding DNA, called enhancers, to control the rate of transcription of genetic information from DNA into the cell.

In disease, alterations in 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 and other transcriptional and regulatory proteins, these proteins are 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.

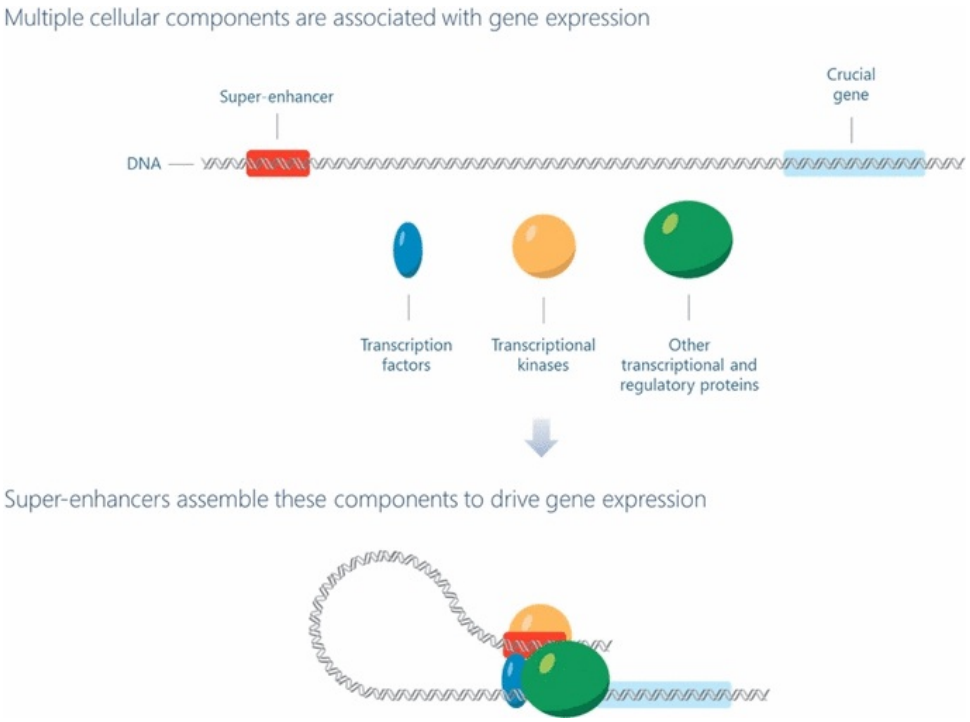
Although researchers have long believed that alterations in non-coding regions of DNA, which account for 98% of the genome, play a key role in driving disease, the scientific community has lacked the tools to study these regions of the genome, rendering them poorly understood. As a result, the discovery 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 identification of new drug targets by sequencing coding regions of DNA has been largely exhausted. Moreover, in cancer, inhibiting abnormal proteins resulting from single genetic alterations can often lead to drug resistance and limited durable clinical benefit. 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.

In contrast to therapies that target a single abnormal protein, gene control medicines target the cell's underlying gene expression program, influencing the expression of the crucial set of genes that contribute to 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 estrogen receptors in breast cancer, androgen receptors in prostate cancer and glucocorticoid receptors 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 and is prescribed 1.9 million times annually in the United States, 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. 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. The findings from Young's three original publications on super-enhancers have been cited in approximately 1,000 subsequent publications since they were published in the scientific journal *Cell* in 2013.

The graphics below illustrate the components and structure of super-enhancers, which drive the expression of genes that are crucial to cell 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.

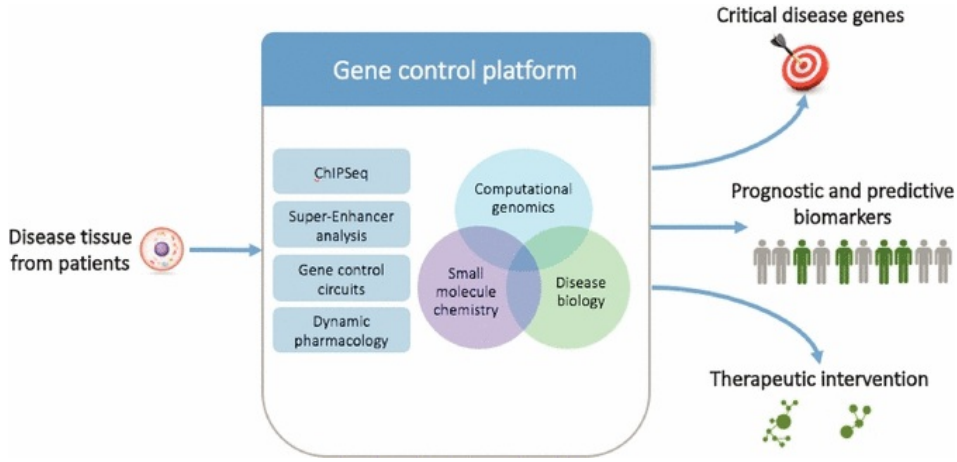
Our Gene Control Platform

Our proprietary gene control platform consists of two fundamental pillars:

- *Identifying novel gene control targets linked to genomically defined patient populations.* We analyze gene expression programs in diseased and healthy cells taken from patient tissues to identify disease-causing

alterations that represent optimal points of therapeutic intervention and associated biomarkers in specific patient populations.

- *Drugging gene control targets.* We develop product candidates to modulate these 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.



Identifying Novel Gene Control Targets

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 biologies. We have in-licensed intellectual property from the laboratories of our scientific founders at the Whitehead Institute and 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. In addition, we are developing our own intellectual property related to this technology. These advancements have enabled us to generate one of the largest known datasets of gene expression programs and identify novel targets across many diseases and cell types. To date, we have analyzed or are in the process of analyzing gene expression programs in AML, breast cancer, ovarian cancer, hepatocellular carcinoma, pancreatic cancer, renal cell carcinoma, glioblastoma, immune cells from the tumor microenvironment, non-disease and lupus immune cells, polycystic kidney disease, spinal muscular atrophy and Alzheimer's disease. Through those efforts, we have identified novel drug targets in oncology, immuno-oncology and autoimmune 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 candidate SY-1425 as well as additional novel preclinical drug candidates in earlier stages of research and development. We plan to analyze gene expression programs in several other cancers, including colorectal, lung and melanoma as well as several other diseases and cell types, including additional inflammatory disorders and immune cells from tumors. 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.

Analyzing Gene Expression Programs in Disease

Generated and Ongoing	Planned
AML	Additional cancers
Breast cancer	Other inflammatory disorders
Ovarian cancer	Other rare genetic diseases
Hepatocellular carcinoma	
Pancreatic cancer	
Renal cell carcinoma	
Glioblastoma	
Immune cells from the tumor microenvironment	
Normal immune cells	
Systemic lupus erythematosus	
Polycystic kidney disease	
Spinal muscular atrophy	
Alzheimer's disease	

We use our platform to pinpoint crucial genes in disease. We compare gene expression programs in diseased cells versus healthy cells and analyze the cells of different patient subsets within a disease to identify novel drug targets linked to genomically defined subsets of patients. We obtain human disease tissue samples from our network of academic collaborators and commercial providers. We then analyze these samples using a variety of genomic tools, including chromatin immunoprecipitation followed by whole genome sequencing, or ChIP-seq, and proprietary computational methods. The combination of these tools allows us to identify the location of DNA elements, including super-enhancers and their associated genes, on the genome. We validate this potential pool of targets by using biological methods for knocking down or out the target gene in cell lines, or by testing existing drugs against a specific target, to determine if the target represents an attractive point of therapeutic intervention.

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 cancer, including genes important in proliferation, invasion and metastasis and immune avoidance, in cancer cells from patient tissue samples. In breast cancer, we were able to recapitulate current knowledge of disease biology and identify clinically validated targets. We analyzed tissue samples from patients with three different types of breast cancer, HER2+, ER+ and triple negative. In HER2+ breast cancer patient samples, we successfully identified a super-enhancer associated with the *ERBB2* gene, which when overexpressed can lead to HER2+ breast cancer.

Similarly, in ER+, or estrogen receptor-positive, breast cancer patient samples, super-enhancers were associated with the *ESR1* gene, which produces estrogen receptor. Therapies targeting the proteins encoded by the *ERBB2* and *ESR1* genes include highly successful marketed drugs, such as Herceptin (trastuzumab) for HER2+ breast cancer and tamoxifen for ER+ breast cancer. Using our platform, we also identified novel drug targets in subsets of patients with HER2+ and ER+ breast cancer and TNBC. Notably, the super-enhancer associated with *RARA*, which we also

discovered in subsets of AML and MDS patients and is the focus of our SY-1425 program, was found in subsets of patients across all three types of breast cancer.

Drugging Gene Control Targets

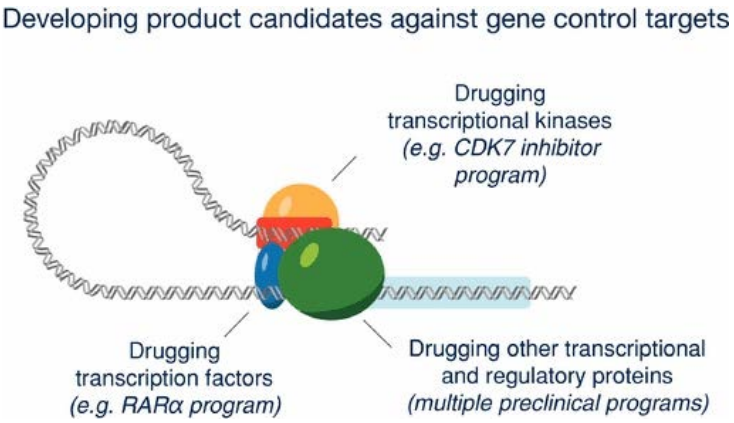
We develop product candidates against gene control targets through:

- 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 designed 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 created the first selective, small molecule inhibitor of CDK7 with *in vivo* efficacy.

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. Using our capabilities and expertise in X-ray crystallography and medicinal chemistry, we are developing proprietary atomic-level knowledge of the structural determinants of transcription factor

inhibition by small molecules. We have generated novel molecules that are in early preclinical development and show biophysical evidence of potent direct transcription factor binding and robust cellular activity.

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 our SY-1425 program. We expect this approach to enable us to more rapidly enter clinical development by accessing compounds that serve as accelerated starting points for our own programs.

Advantages of our Platform and Approach

We believe that there are significant advantages to systematically identifying and drugging gene control targets for specific patient populations. Among these advantages are:

- **Systematic, reproducible and unbiased approach to identifying core disease drivers in multiple serious diseases.** We take a disease-centric approach. We start with human tissue and, through our platform, systematically identify the core drivers of disease. We identify optimal therapeutic points of intervention in a target- and pathway-agnostic manner, opening up a wide array of potential new drug targets.

- **Highly differentiated and pioneering approach with broad applicability across therapeutic areas and diseases.** We are pioneering the understanding of the non-coding, regulatory region of the genome, which has been largely unexploited for drug discovery and development, to uncover novel disease drivers in genomically defined patient populations and advance a new wave of medicines that have the potential to control the expression of disease-driving genes. We have built a differentiated combination of expertise, capabilities and tools to create medicines targeting transcription factors, transcriptional kinases and other transcriptional and regulatory proteins, which have been historically difficult to drug. Because gene expression is fundamental to the function of all cells, we believe that our platform has broad applicability across therapeutic areas and diseases.

- **Ability to discover and develop medicines that address significant patient need.** We are initially focused on difficult-to-treat cancers or cancer subtypes for which current therapies are inadequate. Because gene control medicines affect multiple disease-driving genes, we believe they will be less susceptible to the development of drug resistance than other types of genomic-based targeted medicines, potentially resulting in a more profound and durable benefit for patients. This is evidenced by the proven durable benefits of the gene control medicines available today.

- **Potential for efficient clinical development.** We intend to enrich our clinical trials with genomically defined subsets of patients who are most likely to respond to our drug candidates, which we believe will enable us to determine if there are strong signals of efficacy early in clinical development and well before investments are made in expensive late-stage clinical studies. Subject to encouraging clinical results, we could be eligible to apply for Breakthrough Therapy designation and Fast Track designation which, if granted, could accelerate clinical development and regulatory review, allowing us to bring our therapies to patients expeditiously.

Our Clinical Programs

SY-1425

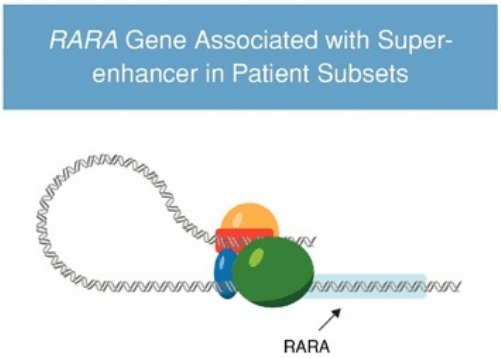
Overview

SY-1425 (tamibarotene) is an oral, potent and selective agonist of the transcription factor RARα. In September 2015, we in-licensed from TMRC the exclusive right to develop and commercialize SY-1425 for oncology indications in North America and Europe. In September 2016, we initiated a Phase 2 clinical trial enrolling genomically defined

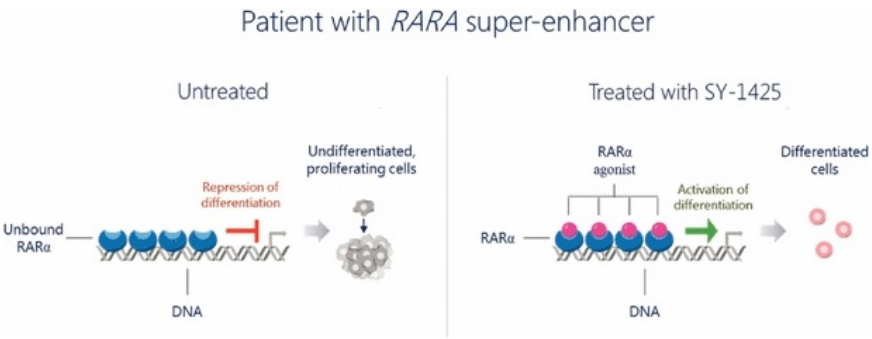
subsets of patients with relapsed or refractory AML and relapsed high-risk MDS pursuant to an IND accepted by the FDA in May 2016. We plan to select patients for this trial using the *RARA* biomarker we identified or another exploratory *RARA* pathway biomarker. We believe patients whose tumors have these biomarkers will be more likely to experience a profound and durable clinical benefit from treatment with SY-1425. In the fourth quarter of 2016, an investigational device exemption for the assay being used to select patients with these biomarkers for inclusion in this trial was approved by the FDA. With this approval, we have expanded this trial to include newly diagnosed AML patients who are at least 60 years old and are not suitable candidates for standard chemotherapy, and lower-risk, transfusion-dependent MDS patients. During 2017, we intend to further expand this trial to explore the safety and efficacy of SY-1425 when combined with azacitidine, a hypomethylating agent that is commonly used to treat AML, in newly diagnosed AML patients who are at least 60 years old and not suitable candidates for standard chemotherapy. We also plan to expand our SY-1425 clinical development program to Europe during 2017.

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, as illustrated in the graphic below.

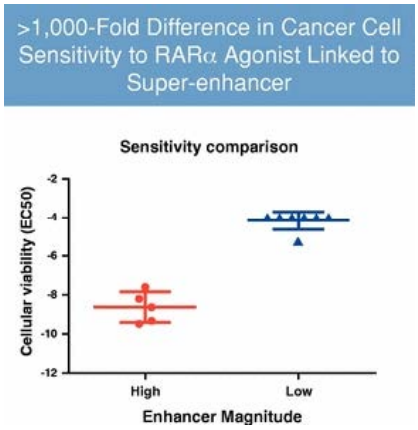


SY-1425 is an oral, selective RARα agonist. Based on experiments we conducted, we have concluded that the mechanism of action of SY-1425 on non-APL AML cells with the *RARA*-associated super-enhancer is very similar to the mechanism of approved retinoic acid agonists in APL, a subset of AML with a genetic alteration of the *RARA* gene.

Specifically, at the American Society of Hematology Annual Meeting and Exhibition held in December 2016, or ASH 2016, we presented data showing that SY-1425 induced significant transcriptional and epigenomic changes in *in vitro* studies of AML cells with high levels of *RARA* gene expression, and that these changes were similar to those seen in APL cells that were treated with SY-1425. In this study, SY-1425 did not induce these changes in AML cells with low levels of *RARA* gene expression. We believe that the consistent biological responses in AML cells with high *RARA* gene expression and APL support the clinical potential of SY-1425 in *RARA* biomarker-positive AML and MDS patients.

We selected SY-1425 based on its superior potency on RARα, its selectivity for RARα over related proteins RARβ and RARγ and its superior pharmacokinetic profile compared to all trans retinoic acid, or ATRA, a pan-agonist of RARα, RARβ, and RARγ. Tamibarotene, the active pharmaceutical ingredient of SY-1425, is approved in Japan under the trade name Amnolake for the treatment of acute recurrent or intractable acute promyelocytic leukemia, or APL, for which it has demonstrated efficacy and a well-established safety profile.

Through our platform, we have identified a biomarker for the super-enhancer associated with *RARA* that we are using for patient selection. Our *in vivo* studies demonstrated that cancer cells with the *RARA* biomarker showed reduced rates of proliferation and differentiated to more mature cells when treated with SY-1425, while cancer cells without the biomarker continued to proliferate. Our studies also demonstrated that cancer cells with the *RARA* biomarker were up to 1,000 times more sensitive to SY-1425 than cancer cells without the biomarker, as shown below. This sensitivity was consistent across multiple cancer cells lines.

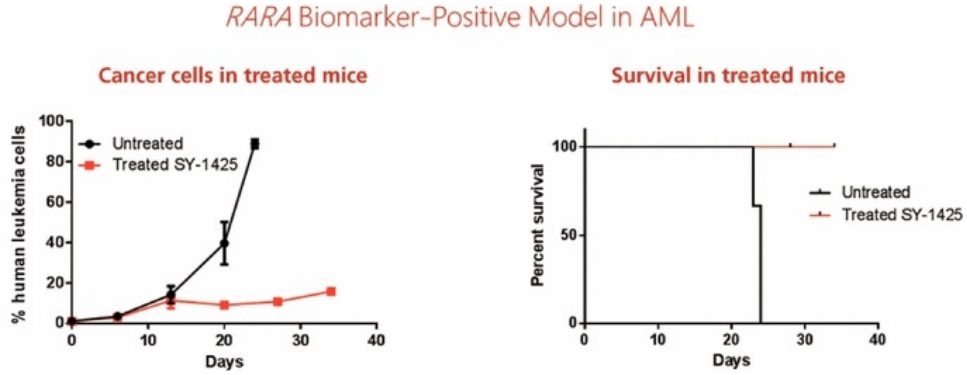


Our Preclinical Data

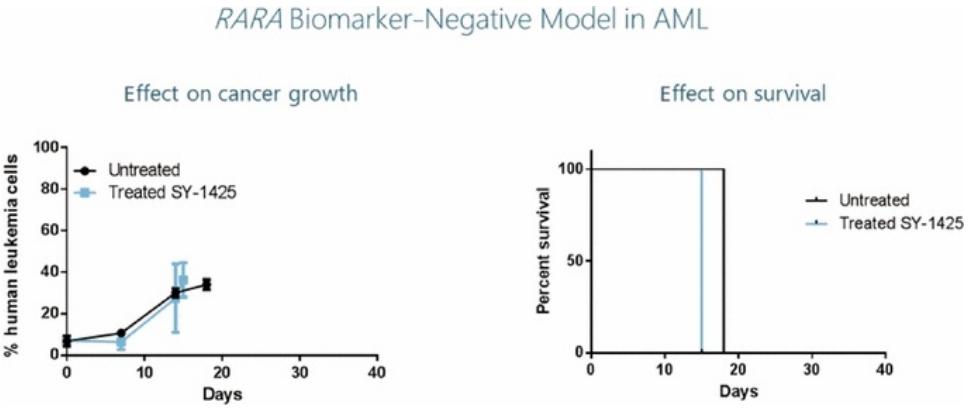
We have conducted multiple preclinical studies of SY-1425 in AML, excluding APL, and in breast cancer. In certain studies, we use mouse models in which mice are implanted with human tumors, which are referred to as patient-derived xenograft models, or PDX models. In PDX models of AML, SY-1425 was observed to be effective in reducing the growth of tumors and prolonging survival in mice with tumors with the *RARA* biomarker, but did not appear to stop tumor growth or prolong survival in mice whose tumors did not have the biomarker.

As shown below, in a PDX model derived from AML patient tumor cells with the *RARA* biomarker, referred to as *RARA* biomarker-positive AML, half of the mice were treated with SY-1425, and the other half of the mice went untreated. In the untreated group, the cancer progressed, as measured by the percentage of human leukemia cells in the blood. Correspondingly, high levels of these cancer cells were measured in the bone marrow and spleen of the untreated mice. None of the untreated mice in the study survived beyond 25 days. In contrast, the cancer was observed to be controlled in the mice treated with SY-1425, as measured by the levels of human leukemia cancer cells detected in the

blood. Similarly, low levels of these cancer cells were measured in the bone marrow and spleen. Notably, all of the mice treated with SY-1425 survived until the end of the 35-day study.



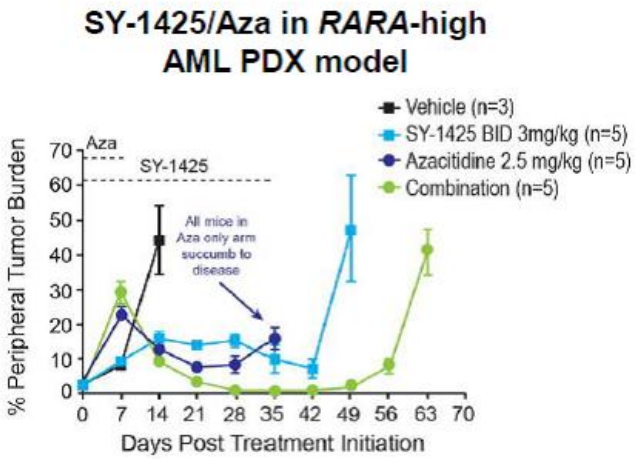
In contrast, as shown below, in a PDX model without the *RARA* biomarker, SY-1425 was observed to have no effect on tumor control or survival. In both the treated and untreated groups, the cancer progressed, as measured by the percentage of human leukemia cells detected in the blood. Correspondingly, high levels of these cancer cells were measured in the bone marrow and spleen in both groups of mice. None of the mice in either group survived beyond 20 days. These data demonstrate a strong link between the *RARA* biomarker and response to treatment with SY-1425, and provide meaningful evidence that patients with the *RARA* biomarker may be promising candidates for a clinical trial of SY-1425.



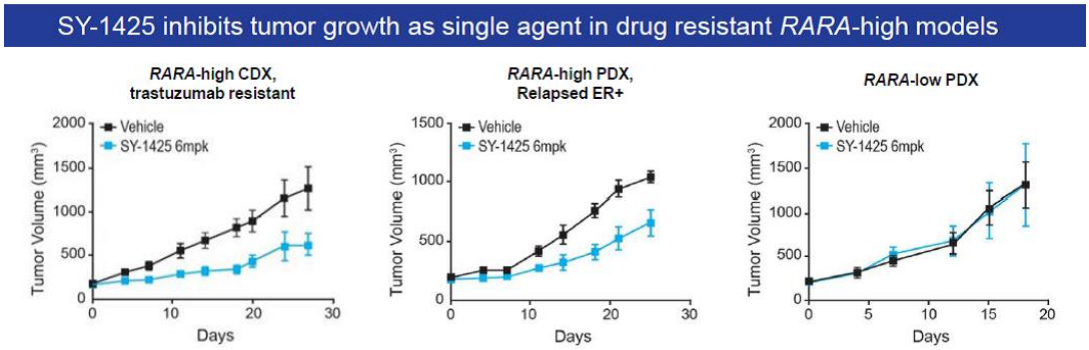
We have also compared the activity of SY-1425 to the activity of ATRA in the *RARA* biomarker-positive PDX model. We observed superior anti-tumor activity and survival with SY-1425 compared to ATRA, with ATRA-treated mice demonstrating similar survival to the untreated mice.

At ASH 2016, we also presented data showing that SY-1425 increased the anti-tumor activity of chemotherapy and hypomethylating agents in *in vivo* models of AML with high levels of *RARA* gene expression. Administration of SY-1425 was shown to result in greater tumor growth inhibition and duration of response when used in combination with

azacitidine, compared to either azacitidine or SY-1425 alone, in a *RARA* biomarker-positive PDX model. These data are shown below:



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.



SY-1425 Clinical 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 the *RARA* biomarker. In September 2016, we initiated a multi-center, open-label Phase 2 clinical trial enrolling genomically defined subsets of patients with relapsed or refractory AML and relapsed high-risk MDS pursuant to an IND accepted by the FDA in May 2016. We are selecting patients for this trial using the *RARA* biomarker we identified or another exploratory *RARA* pathway biomarker. We believe patients whose tumors have these biomarkers will be more likely to experience a profound and durable clinical benefit from treatment with SY-1425.

In the fourth quarter of 2016, an investigational device exemption for the assay being used to select patients with the *RARA* pathway biomarkers for inclusion in this trial was approved by the FDA. With this approval, we have expanded this trial to include newly diagnosed AML patients who are at least 60 years old and are not suitable candidates for standard chemotherapy, and lower-risk, transfusion-dependent MDS patients. We believe SY-1425 is ideally suited for these patient groups because, in contrast to cytotoxic chemotherapy, it has been generally well tolerated in a related patient population with APL, and because SY-1425 is orally administered and has the potential to be used chronically.

Based on supporting preclinical data, we intend to further expand this trial during 2017 to explore the safety and efficacy of SY-1425 when combined with azacitidine, a hypomethylating agent that is commonly used to treat AML, in newly diagnosed AML patients who are at least 60 years old and not suitable candidates for standard chemotherapy.

We anticipate that we will enroll approximately 100 patients in this trial in the aggregate, each of whom will have been prospectively selected using our *RARA* biomarker or another exploratory *RARA* pathway biomarker. The primary endpoint in the AML and high-risk MDS cohorts of the trial is overall response rate and in the lower-risk MDS cohort of the trial is transfusion independence. We also plan to measure pharmacodynamic markers, duration of response, safety and tolerability, survival and biomarker predictability. Data regarding two of these pharmacodynamic markers, *DHRS3* and *CD38*, were presented at ASH 2016. *DHRS3* expression was shown to be induced by administration with SY-1425 in AML cells with high *RARA* gene expression and to be correlated with anti-proliferative effect and expression of *CD38* was significantly increased in response to administration of SY-1425. We continue to expect to report initial data from this trial approximately 12 months after the first patient was enrolled, or in the fall of 2017.

We have entered into an agreement with a third party commercial provider to continue developing our novel *RARA* biomarker into a validated laboratory test under Clinical Laboratory Improvement Amendment, or CLIA, guidelines using a well-established diagnostic platform and approach that may be used to prospectively enroll *RARA* biomarker-positive patients in our clinical trial. In the fourth quarter of 2016, an investigational device exemption was approved by the FDA for this test. 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 the *RARA* biomarker, 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 2017.

Tamibarotene, the active pharmaceutical ingredient of SY-1425, has been extensively studied and has a well-established safety profile. In our ongoing Phase 2 clinical trial, we are using the same dosage used in the treatment of 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 for all cancer indications the preclinical data package that was used for approval in Japan and the IND filing in the United States.

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. 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 plan to initiate clinical trials in these patients upon establishing proof-of-concept in AML and MDS. 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.

Existing 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 four-year relapse-free survival rate in high-risk patients treated with tamibarotene was 87%, compared to 58% in high-risk patients treated with ATRA (p=0.028).

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/m² 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]	269	Front-line following ATRA-induced CR and consolidation	Tamibarotene 6 mg/m² vs. ATRA 45 mg/m² 14 days every 3 months for 2 years	Overall 4-year RFS: 91% vs. 84%; 4-year RFS in high risk: 87% vs. 58% (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/m² 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/m²/day tamibarotene, 25 mg/m²/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. Shinagawa, et al. *Journal of Clinical Oncology*, November 2014.
3. Sanford D, et al. *British Journal of Haematology*, July 2015.
4. Wang et al, ASH 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 (Levitt DJ et al J Clin Oncol 34, 2006 (suppl; abstr e20560)).

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. Based on our analysis of super-enhancers associated with *RARA* in patient samples, and on *RARA* biomarker data in publicly available databases, we estimate that approximately 25% of AML and MDS patients and approximately 35% of breast cancer patients may benefit from RARα agonist therapy like SY-1425.

There are an estimated 33,000 new AML diagnoses in the United States, Canada and the five largest European countries each year. AML remains an area of significant unmet medical need. In the United States, newly diagnosed patients have a 27% five-year survival rate. There has been little improvement in treatment options for AML in the past 20 years, with typical treatment including older chemotherapeutics and stem cell transplantation. Nearly half of newly diagnosed patients, or approximately 16,000 patients, are elderly or unfit for treatment with standard therapies, leaving this group with very few to no treatment options.

Of the estimated 33,000 newly diagnosed patients each year in the countries listed above, approximately 30%, or 10,000, AML patients relapse or become refractory to current treatment options. In the absence of adequate therapies, these relapsed or refractory patients may be put into clinical trials for new and emerging therapies.

Based on our analysis of super-enhancers associated with *RARA* in patient samples and on *RARA* biomarker data in publicly available databases, we believe that approximately 25% of AML patients could benefit from treatment with a RARα agonist such as SY-1425. Thus, we estimate that in the countries listed above, approximately 2,500 patients who eventually relapse or are refractory to current treatment options and 4,000 patients who are elderly or unfit for standard treatments could benefit from treatment with a RARα agonist such as SY-1425.

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. In the United States, high-risk patients have a median survival of only approximately two years, while the lower-risk patient population has a median survival of approximately six years. As with AML, treatment options are limited. More than half of the newly diagnosed patients, or approximately 17,000 patients, have lower-risk transfusion-dependent MDS.

Of the estimated 32,000 newly diagnosed patients in the countries listed above each year, approximately 19% or 6,000 MDS patients have relapsed or refractory high-risk MDS.

Based on *RARA* biomarker data in publicly available databases, we believe that approximately 25% of MDS patients could benefit from treatment with a RARα agonist such as SY-1425. Thus, we estimate that in the countries listed above, approximately 1,500 patients diagnosed with relapsed or refractory high-risk MDS each year and 4,250 patients diagnosed with lower-risk transfusion-dependent MDS each year could benefit from treatment with a RARα agonist such as SY-1425.

Approximately 485,000 women in the countries listed above are diagnosed with breast cancer annually. Approximately 158,000 of these women are categorized as metastatic and, therefore, eligible for systemic therapies. Breast cancer is categorized and treated by the stage for risk of metastatic recurrence and by whether it is driven by estrogen receptor and progesterone receptor signaling, referred to as being hormone positive, driven by HER2 receptor signaling, referred to as being HER2+, or neither, which is referred to as being triple negative. Despite advances in treatments for hormone-positive and receptor-positive patients, the lack of similar advances in treatment options for TNBC patients, which represent approximately 15 to 20% of all newly diagnosed breast cancer patients each year in the countries listed above, represents a significant unmet medical need. In the United States, the five-year survival rate of newly diagnosed metastatic breast cancer is approximately 26%. In the United States, 40,000 women die annually from breast cancer, making breast cancer one of the largest causes of cancer-related deaths. Based on our analysis of patient samples, we believe that approximately 35% of metastatic patients, or 55,000 patients in the countries listed above, have the *RARA* biomarker and would benefit from a product candidate like SY-1425.

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, the disease remains associated with a significant incidence of early death due to disease-related susceptibility to bleeding or hemorrhage.

SY-1365

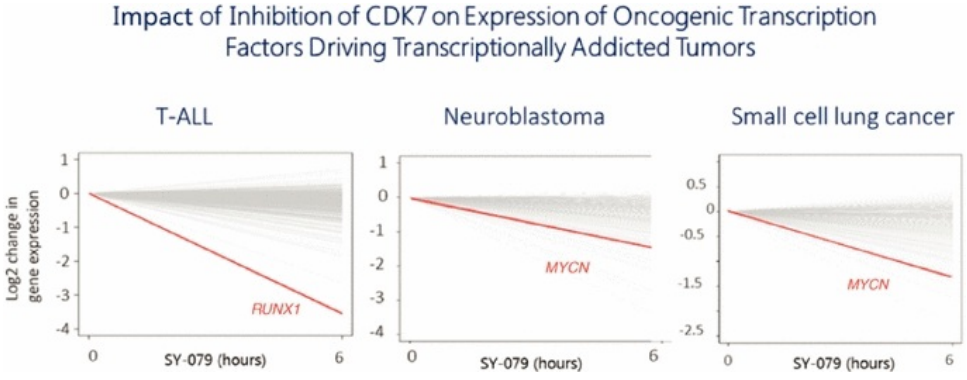
Overview

SY-1365 is a highly potent and selective small molecule CDK7 inhibitor focused on cancers that are dependent on a high and constant expression of certain transcription factors for their growth and survival, a phenomenon known as transcriptional addiction. Using our platform, we have generated several potent and selective small molecule CDK7 inhibitors, including SY-1365. We chose SY-1365 as our development candidate based on its promising efficacy and safety observed in our preclinical studies. We have completed IND-enabling activities for SY-1365 and plan to initiate a Phase 1 clinical trial in patients with advanced solid tumors in the second quarter of 2017.

Drugging Transcriptional Kinases

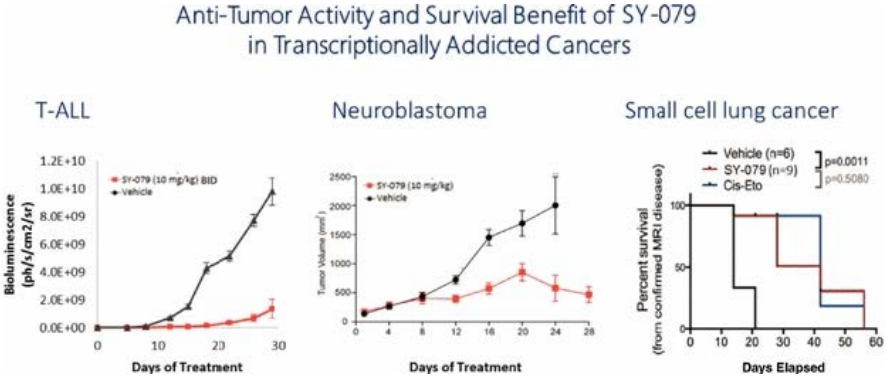
Using our CDK7 inhibitor SY-079, known in the scientific literature as THZ1, a "tool" or research compound, our scientific founders and collaborators demonstrated that transcriptionally addicted cancers are particularly sensitive to selective inhibition of CDK7. CDK7, a member of the cyclin-dependent kinase, or CDK, family, is a transcriptional kinase that plays a central role in the expression of transcription factors in these cancers. CDK7 is associated with super-enhancers that control the expression of the transcription factors driving the cancer's growth and survival. Inhibiting CDK7 preferentially lowers the expression of disease-driving transcription factors controlled by super-enhancers, and results in the selective killing of cancer cells over non-cancerous cells.

Our scientific founders and collaborators conducted preclinical studies in cell lines of T-ALL, a form of ALL that originates in T-cells, *MYCN*-amplified neuroblastoma, a form of neuroblastoma resulting from amplification of the gene *MYCN*, and small cell lung cancer. As shown in the graphic below, CDK7 inhibition resulted in reduced expression levels of the specific transcription factor contributing to each of these cancers: *RUNX1* in T-ALL and *MYCN* in neuroblastoma and small cell lung cancer. These findings have been published in *Cell*, *Nature* and *Cancer Cell*.

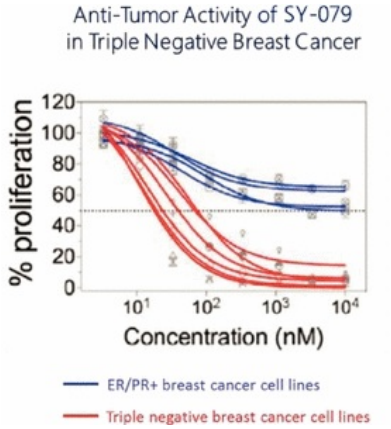


As shown below, in additional preclinical studies conducted by our scientific founders and collaborators, SY-079 also demonstrated significant anti-tumor activity in cell line-derived, or CDX, models of T-ALL and *MYCN*-amplified neuroblastoma, as well as a survival benefit similar to chemotherapy in a genetically engineered mouse model of small cell lung cancer. In the T-ALL model, the tumor size was measured by the bioluminescence, or the aggregate brightness of chemically tagged tumor cells in an imaging study. In the *MYCN*-amplified neuroblastoma

model, tumor size was estimated by total volume. In the small cell lung cancer model, researchers demonstrated a survival benefit similar to chemotherapy in genetically engineered mice treated with SY-079.



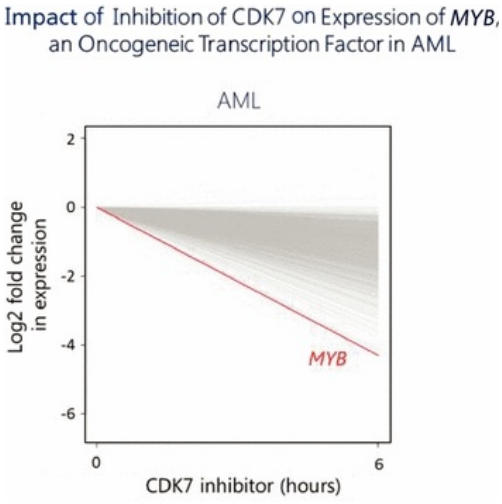
Our scientific founders and collaborators have also demonstrated the strong potential of CDK7 inhibition, using SY-079, as a novel treatment strategy for TNBC, a highly aggressive form of breast cancer that is transcriptionally addicted. In a PDX model of TNBC, SY-079 selectively impacted the expression of a set of crucial genes, killing cancer cells and inhibiting tumor growth. This exemplifies our gene control approach of influencing multiple crucial genes driving cancer with one inhibitor in a targeted fashion. The graphic below illustrates the impact of increased exposure of SY-079 on cell growth on ER/PR+ breast cancer cell lines as compared to TNBC cell lines.



As illustrated above, SY-079 was observed to have a dramatic impact on cell growth in TNBC cell lines, as measured by the estimated percentage of proliferating cells. The ER/PR+ breast cancer cell lines were significantly less sensitive to treatment with SY-079. These findings were published in *Cell*.

In an AML cell line treated with a CDK7 inhibitor, expression levels of genes associated with super-enhancers that we studied were observed to be more highly repressed on average than those of the genes we studied that are not associated with super-enhancers. In this same cell line, *MYB* was observed to be one of the most highly repressed genes.

We believe this finding is significant because *MYB* is a transcription factor gene known to contribute to AML. Notably, we have identified super-enhancers associated with *MYB* in nearly all AML patient samples we have analyzed.



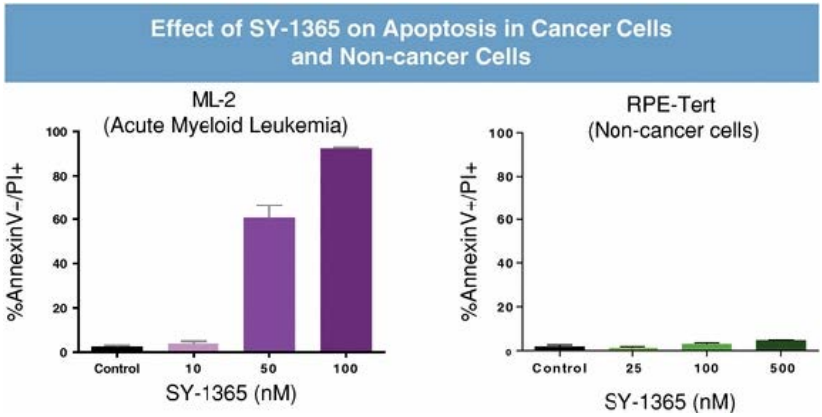
Our Preclinical Data

Using our internal drug discovery capabilities, we have generated several potent and selective small molecule CDK7 inhibitors, including SY-1365, with significantly enhanced drug-like characteristics over SY-079. Our CDK7 inhibitors are covalent, meaning that they bind irreversibly and selectively to CDK7. We believe that selectivity is critical for a therapeutic index with CDK inhibition. CDK inhibitors known as pan-CDK inhibitors are not selective for a specific CDK. Though they have demonstrated anti-tumor activity, pan-CDK inhibitors have limited clinical utility due to dose-limiting toxicities. More recently, a selective inhibitor of CDK4/6, members of the CDK family involved in cell cycle, received accelerated approval in breast cancer, demonstrating the substantial clinical benefit of selective CDK inhibition.

We have conducted a comprehensive set of biochemical and cellular experiments to characterize the potency and selectivity of SY-1365. In those experiments, SY-1365 demonstrated high biochemical and cellular potency with a high degree of selectivity. When SY-1365 was scanned against a panel of 468 kinase assays, it was observed to demonstrate significant binding, defined as 90% binding at a concentration of 1 μm, to only seven kinases, including CDK7. Notably, SY-1365 was not observed to significantly bind to members of the CDK family involved in cell cycle.

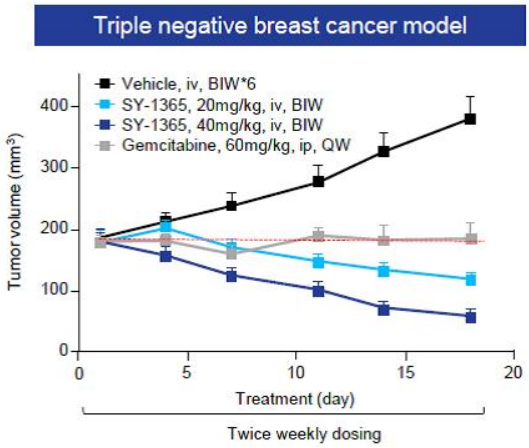
SY-1365 has been observed to selectively kill cancer cells in AML and ALL cell lines by inducing robust and sustained apoptosis, or programmed cell death. As shown below, in a comparative assay measuring a marker of apoptosis, SY-1365 preferentially kills cancer cells in AML, with a clear dose effect, meaning that as we increased the

concentration of the drug, more apoptosis was observed. There was, however, relatively little effect on non-cancerous cells regardless of dose.



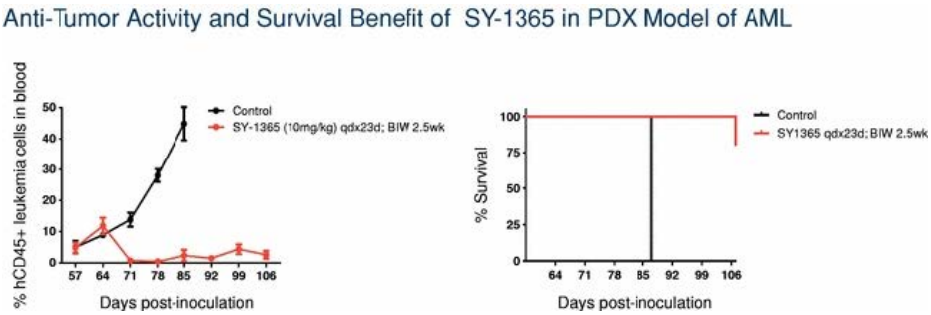
In *in vivo* studies that we conducted, SY-1365 was observed to induce tumor regression in a xenograft model of TNBC, and to have complete responses and survival benefit in models of AML.

As shown in the graphic below, SY-1365 was observed to result in tumor regression in a xenograft model of TNBC when dosed twice weekly, which is the dosing regimen we expect to use in our planned Phase 1 clinical trial of SY-1365. The treated mice were observed to maintain a stable body weight, which is an indicator of a promising safety profile, as well as an indicator of preclinical efficacy.

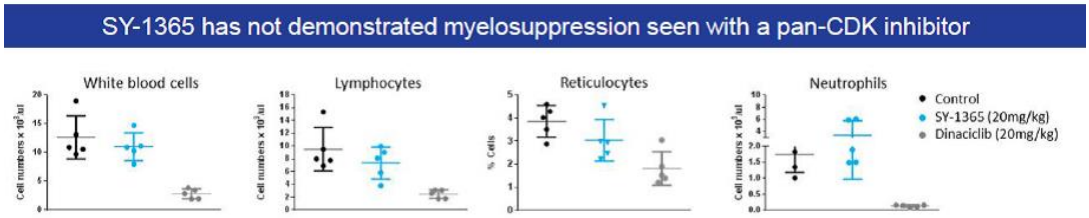


SY-1365 was also observed to have significant anti-tumor activity and survival benefit in a PDX model of AML, as shown in the graphic below. In this study, treated mice received a 10 mg/kg dose of SY-1365 daily for the first 23 days of the study and then were dosed intermittently, twice per week, through the 39th day of the study. Mice treated with SY-1365 in this model experienced initial clearance of the disease and maintained residual low levels of human leukemia cells. As in the TNBC model above, the treated mice in this study were observed to maintain a stable body weight. In fact, beyond the dosing period, 80% of treated mice remained alive, and levels of human leukemia cells in the blood remained at less than 5%. By contrast, in the untreated mice, the cancer progressed, reaching levels of human

leukemia cells of greater than 50% in blood and greater than 90% in tissues, at which point all mice had died of their disease or were humanely sacrificed due to excessive tumor burden.



In preclinical studies, SY-1365 was observed to have markedly fewer negative effects on healthy cells than a pan-CDK inhibitor. Pan-CDK inhibitors have been observed to result in blood cell death, or myelosuppression. As shown in the graphic below, when we compared the effect of SY-1365 on four types of blood cells in mice to the effect of a pan-CDK inhibitor being developed for cancer, known as dinaciclib, the mice treated with SY-1365 did not demonstrate the same level of myelosuppression that occurred in mice treated with dinaciclib. Based on this data, we believe that SY-1365 will have a more favorable safety profile than pan-CDK inhibitors.



Immunocompetent wild-type Balb/c, 8 week old female mice were treated qdx5 with vehicle, Syros compound and Dinaciclib, a known pan-kinase inhibitor. Day 6 complete blood counts were analyzed and plotted (n=5/group).

SY-1365 was observed to reduce expression of cancer-contributing genes associated with super-enhancers, including oncogenic transcription factors *MYB* and *MYC*, in an AML cell line. Additionally, SY-1365 also showed synergistic activity in *in vitro* models of AML when combined with other targeted agents, including Flt3, Bcl-2 and BET inhibitors.

SY-1365 Clinical Development Plan

We have completed IND-enabling activities for SY-1365. Our goal is to initiate a Phase 1 clinical trial in patients with advanced solid tumors in the second quarter of 2017. Following the dose escalation phase of this study, we plan to open expansion cohorts enriched for transcriptionally driven tumors, including TNBC and ovarian and small cell lung cancers. We anticipate reporting initial data from this study in the first half of 2018, or approximately one year after the first patient is enrolled in the study. We have chosen to enroll patients with advanced solid tumors in our first trial based on the high degree of efficacy observed in our preclinical studies, the high degree of transcriptional dysregulation in TNBC and other select solid tumors, the significant unmet medical need of these patients and the potential for accelerated development. We then plan to expand into a broader set of molecularly defined patient populations using our gene control platform, including acute leukemias such as AML and ALL.

We are leveraging our platform to identify biomarkers that will predict patients most likely to respond to SY-1365. We intend to use a pharmacodynamics marker of target engagement in the tumor to guide our dosing in clinical trials.

SY-1365 Market Opportunity

With SY-1365, we believe we have the opportunity to address significant unmet medical needs across a range of transcriptionally addicted blood cancers and solid tumors. We will initially pursue clinical development of SY-1365 in solid tumors, including TNBC and ovarian and small cell lung cancers.

There are an estimated 42,000 metastatic TNBC 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. Despite advancements in treatments for HER2+ and ER+ breast cancer, the lack of similar advancements in the treatment of TNBC, which represents approximately 15-20% of all newly-diagnosed breast cancer patients each year in the developed pharmaceutical markets, represents a significant unmet medical need. In the United States, the five-year survival rate of newly-diagnosed metastatic breast cancer patients is approximately 26%.

There are an estimated 60,000 metastatic ovarian cancer diagnoses each year in the developed pharmaceutical markets. In the United States, the five-year survival rate of metastatic ovarian cancer is approximately 17%. Likewise, there are an estimated 65,000 metastatic small cell lung cancer diagnoses each year in the developed pharmaceutical markets, and the five-year survival rate of metastatic small cell lung cancer patients in the United States is approximately 2%.

Our planned Phase 1 clinical trial of SY-1365 will be in patients with advanced solid tumors, with expansion cohorts enriched for transcriptionally driven tumors, including TNBC and ovarian and small cell lung cancers. In the course of this trial, we plan to use our platform to identify biomarkers that could enable us to identify subsets of these patients who are most likely to benefit from SY-1365. Over time, we plan to evaluate SY-1365 in transcriptionally-addicted blood cancers where there is a high mortality rate, high unmet medical need and few, if any, treatment options, including AML and ALL.

There are an estimated 37,000 new AML diagnoses each year in the developed pharmaceutical markets. In the United States, newly diagnosed patients have a 27% five-year survival rate. There has been little improvement in treatment options for AML in the past 20 years, with typical treatments including older chemotherapeutics and stem cell transplantation. AML remains an area of significant unmet medical need. Our initial clinical trial will include patients with relapsed and refractory AML and patients who are elderly or unfit for treatment with standard therapies. We estimate this population to be 29,000 patients, of which 11,000 patients have relapsed or refractory AML and of which 18,000 patients are elderly or unfit for treatment with standard therapies.

ALL is characterized by an excess of lymphoblastic cells, and approximately 12,000 patients are diagnosed annually in the developed pharmaceutical markets. Approximately 60% of patients diagnosed with ALL are younger than 20 years old. Eighty percent of these patients are cured by current treatments such as chemotherapy and stem cell transplantation. Only approximately 50% of patients older than 20 years old are cured, however, highlighting the need for more effective therapies. Our initial clinical trial will include adult recurrent or refractory patients. We estimate there are 2,500 such patients in the developed pharmaceutical markets.

Other Programs

We currently have four programs in our early preclinical pipeline, including programs directed to the development of a CDK7 inhibitor that can be administered orally, inhibitors of cyclin-dependent kinase 12/13, and two other programs in the fields of cancer and immuno-oncology. We plan to advance at least one of these preclinical programs 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 across additional cancers, inflammatory diseases, rare genetic disorders, and other diseases to identify optimal points of therapeutic intervention in specific subsets of patients and to create a pipeline of novel preclinical drug candidates targeting transcriptional and regulatory proteins, as well as to link existing drugs to novel genomically defined patient populations. In particular, during 2017 we intend to enhance our platform to focus on analysis of the regulatory genomic elements controlling single gene expression for rare cancers and genetic diseases.

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 December 31, 2016, we own four pending U.S. provisional patent applications, six U.S. pending patent applications, 29 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 December 31, 2016, we have exclusively licensed four issued U.S. patents, seven U.S. pending patent applications, five issued foreign patents and 18 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 December 31, 2016 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

The intellectual property portfolio for SY-1425 contains one U.S. pending patent application that is fast-tracked in the USPTO, one pending PCT patent application and two provisional patent applications directed to patient stratification methods based on biomarkers, combinations and methods of use for agonists of RARα, as well as several licensed patents directed to various aspects of that compound. The U.S. pending application and any U.S. or non-U.S. applications claiming priority to these pending applications, if issued, will have a statutory expiration date of 2036 or 2037.

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 for these novel compounds. As of December 31, 2016, we own four pending U.S. patent applications, 28 pending foreign applications in a number of jurisdictions, including Europe, Canada, China, Japan and Australia and one pending PCT patent application and one pending U.S. provisional application, 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 of October 2034, April 2035, October 2035, or July 2037. Patent term adjustments or patent term extensions could result in later expiration dates.

We are also exclusively licensed under three pending U.S. patent applications and 10 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 in multiple compound families, methods of treating various diseases through inhibition of specific transcription factor(s) and methods of detecting inhibitors or certain transcription factors. As of December 31, 2016, we own two pending PCT patent applications and one U.S. provisional patent application and were exclusively licensed to one issued U.S. patent and two U.S. and two pending foreign patent applications in Europe directed to our other programs. The licensed U.S. patent has a statutory expiration date of July 2032. 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 and their use will have statutory expiration dates of February 2031, August 2032, November 2033, June 2036 and September 2037.

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, and methods for identifying protein binding sites in a genome. As of December 31, 2016, 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, two U.S. pending patent applications and six pending foreign patent applications in a number of jurisdictions, including Australia, Canada, China, Europe and Japan, 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 of 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 of October 2033. The licensed U.S. and foreign patent applications directed to methods for identifying protein binding sites in a genome, if issued, will have a statutory expiration date of June 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 Agreements

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.

Dana-Farber Cancer Institute, Inc.

In February 2013, we entered into a license agreement with Dana-Farber Cancer Institute, Inc., or 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 s 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 the Whitehead Institute for Biomedical Research, or 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 a worldwide, sublicensable with certain restrictions, license under specified patents relating to Chem-Seq or modulators of Myc/Max Screen 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. This license is exclusive, on a patent-by-patent basis in the designated fields, (i) during the term, with respect to patent rights relating to Myc/Max Screen, (ii) during the term, for use of Chem-Seq for human health and therapeutics, (iii) for a period of three years, with respect to Chem-Seq outside of human health and therapeutics and (iv) during the term, for other specified patent rights, with limited exceptions, including non-exclusive rights for research use reagents.

We can automatically extend the period of exclusive rights with respect to Chem-Seq for an additional two years in exchange for an extension payment and we have been granted the first right for a limited extension after such period. 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. Subject to certain restrictions, we were granted an option to obtain an exclusive commercial license to certain improvements created by Whitehead or Dana-Farber during the first three years of the agreement. The option is exercisable within a certain period from the date of disclosure, and the license would be negotiated in good faith and incorporated into this agreement. 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, 2017, 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.

TMRC

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

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

Competition

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

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

The most common methods of treating patients with cancer are surgery, radiation and drug therapy, including chemotherapy, hormone therapy and targeted drug therapy. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. While our product candidates may compete with many existing drug and other therapies, they may also be used in combination with or as an adjunct to these therapies. Some of the currently approved drug therapies are branded and subject to patent protection, and others are available on a generic basis. Many of these approved drugs are well-established therapies and are widely accepted by physicians, patients and third-party payors. In general, although there has been considerable progress over the past few decades in the treatment of cancer and the currently marketed therapies provide benefits to many patients, these therapies

all are limited to some extent in their efficacy and frequency of adverse events. As a result, the level of morbidity and mortality from cancer remains high.

In addition to currently marketed therapies, there are also a number of medicines in late stage clinical development to treat cancer. These medicines in development may provide efficacy, safety, convenience and other benefits that are not provided by currently marketed therapies. As a result, they may provide significant competition for any of our product candidates for which we obtain market approval.

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

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

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

If the drug 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 biomarker. There has been little advancement in treatment options for patients with these cancers. Typical treatment includes chemotherapy followed by stem cell transplantation. SY-1425 may face competition from other drug candidates currently in clinical development for relapsed or refractory AML and MDS, including drug candidates in development from Daiichi Sankyo Company, Limited, Boehringer Ingelheim GmbH, Agios Pharmaceuticals, Inc., Novartis AG, Astellas Pharma Inc., Seattle Genetics, Inc., Celgene Corporation, Janssen Research & Development LLC, Pfizer, Inc., Karyopharm Therapeutics Inc. and Aileron Therapeutics, Inc. 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 and high-risk MDS.

SY-1365

We initially plan to evaluate SY-1365, our CDK7 inhibitor, in patients with advanced solid tumors. We believe that SY-1365 will be the only selective CDK7 inhibitor in clinical development. Because the mechanism of action is different than the others currently on the market and in development, we believe that it could be first-in-class and used in combination with other therapies, which could minimize competition, assuming that data from a registration-enabling trial warrants such use. We are aware of two other selective CDK7 inhibitor programs that we believe to be in early preclinical development.

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.

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

Review and Approval of Drugs in the United States

In the United States, the FDA approves and regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and implementing regulations. The failure to comply with requirements under the FDCA and other applicable laws at any time during the product development process, approval process or after approval may subject an applicant and/or sponsor to a variety of administrative or judicial sanctions, including refusal by the FDA to approve pending applications, withdrawal of an approval, imposition of a clinical hold, issuance of warning letters and other types of letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement of profits, or civil or criminal investigations and penalties brought by the FDA and the Department of Justice or other governmental entities.

An applicant seeking approval to market and distribute a new drug product in the United States must typically undertake the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND, which must take effect 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 in accordance with good clinical practices, or GCP, to establish the safety and efficacy of the proposed drug product for each indication;
- preparation and submission to the FDA of a New Drug Application, or NDA, requesting marketing for one or more proposed indications;
- review by an FDA advisory committee, where appropriate or if applicable;
- satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities at which the product, or components thereof, are produced 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 FDA audits of clinical trial sites to assure compliance with GCPs and the integrity of the clinical data;
- payment of user fees and securing FDA approval of the NDA; 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 post-approval studies.

Preclinical Studies

Before an applicant begins testing a compound with potential therapeutic value in humans, the drug candidate enters the preclinical testing stage. Preclinical studies include laboratory evaluation of product chemistry, toxicity and formulation, as well as *in vitro* and animal studies to assess the potential safety and activity of the drug for initial testing in humans and to establish a rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations. 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, 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, may continue after the IND is submitted.

Human Clinical Trials in Support of an NDA

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators 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 study protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to a proposed clinical trial and places the trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. The FDA can place an IND on clinical hold at any point in development, and depending upon the scope of the hold, clinical trial(s) may not restart until resolution of the outstanding concerns to the FDA's satisfaction.

In addition, 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 a 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.

Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for 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 certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on its ClinicalTrials.gov website.

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators 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 study protocols detailing, among other things, the inclusion and exclusion criteria, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated.

Human clinical trials are typically conducted in the following sequential phases, which may overlap or be combined:

- ***Phase 1.*** The drug is initially introduced into healthy human subjects or, in certain indications such as cancer, patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an early indication of its effectiveness and to determine optimal dosage.

- ***Phase 2.*** The drug is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.

- ***Phase 3.*** The drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the efficacy and safety of the product for approval, to establish the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product.

- ***Phase 4.*** Post-approval studies may be conducted after initial marketing approval. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and more frequently if serious adverse events occur. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions; findings from other studies or animal or *in vitro* testing that suggest a significant risk in humans exposed to the drug; and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The FDA or the sponsor or the data monitoring committee 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 drug 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 drug 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 drug candidate does not undergo unacceptable deterioration over its shelf life.

Review of an NDA by the FDA

Assuming successful completion of required clinical testing and other requirements, the results of the preclinical studies and clinical trials, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the drug product for one or more indications. Under federal law, the submission of most NDAs is additionally subject to an application user fee, and the sponsor of an approved NDA is also subject to annual product and establishment user fees. These fees are typically increased annually. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for drugs with orphan designation and a waiver for certain small businesses, an exception from the establishment fee when the establishment does not engage in manufacturing the drug during a particular fiscal year, and an exception from the product fee for a drug that is the same as another drug approved under an abbreviated pathway.

The FDA conducts a preliminary review of an NDA 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 to determine whether the application is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA 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 NDA 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 drugs that are not NMEs, the ten-month and six-month review periods run from the date that the FDA receives the application. The review process and the Prescription Drug User Fee Act goal date may be extended by the FDA for three additional months to consider new information or clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an NDA, 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 drug component manufacturing (e.g., active pharmaceutical ingredients), finished drug 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.

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 an NME. REMS can include medication guides, physician communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU may 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 patient registries. The FDA may require a REMS before approval or post-approval if it becomes aware of a serious risk associated with use of the product. The requirement for a REMS can materially affect the potential market and profitability of a product.

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

Fast Track, Breakthrough Therapy, Priority Review Designations

The FDA is authorized to designate certain products for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs are 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. The FDA's time period goal for reviewing a Fast Track application does not begin, however, 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 product, 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.

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 withdraw the product from the market on an expedited basis. 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 NDA 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 product, it may limit the approved indications for use for the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess the drug's safety after approval, 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, which can materially affect the potential market and profitability of the product. 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 Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as new application fees for supplemental applications with clinical data.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third-party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards 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 new 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, suspension of the approval, or 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 NDAs or supplements to approved NDAs, 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 marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

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 drugs and prescription drug samples at the federal level, and set minimum standards for the regulation of drug distributors by the states. The PDMA, its implementing regulations and state laws limit the distribution of prescription pharmaceutical product samples, and the DSCA imposes requirements to ensure accountability in distribution and to identify and remove counterfeit and other illegitimate products from the market.

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.

505(b)(2) NDAs

Most NDAs for new drug products are based on two full clinical studies, which must contain substantial evidence of the safety and efficacy of the proposed new product. 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 provision was enacted as part of the Hatch-Waxman Amendments and permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by, or for, the applicant. If the 505(b)(2) applicant can establish that reliance on the FDA's previous findings of safety and effectiveness is scientifically and legally appropriate, it 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, including clinical trials, to support the change from the previously approved reference drug. The FDA may then approve the new product candidate for all, or some, of the label indications for which the reference drug has been approved, as well as for any new indication sought by the 505(b)(2) applicant. 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."

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 or 505(b)(2) 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 or the 505(b)(2) application 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 application 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 applicant. The ANDA or 505(b)(2) application also will not be approved until any applicable non-patent exclusivity listed in the Orange Book for the branded reference drug has expired.

Pediatric Studies and Exclusivity

Under the Pediatric Research Equity Act, an NDA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the drug 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. With enactment of the Food and Drug Safety and Innovation Act, or the FDASIA, in 2012, 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 any 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.

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 and until the FDA promulgates a regulation stating otherwise, the pediatric data requirements do not apply to products with orphan designation.

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including the non-patent and orphan exclusivity. This six-month exclusivity may be granted if an NDA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application. With regard to patents, the six-month pediatric exclusivity period will not attach to any patents for which an ANDA or 505(b)(2) applicant submitted a paragraph IV patent certification, unless the NDA sponsor or patent owner first obtains a court determination that the patent if valid and infringed by the proposed product.

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may designate a drug product as an "orphan drug" if it is intended to treat a rare disease or condition, generally meaning that it affects fewer than 200,000 individuals in the United States, or more in cases in which there is no reasonable expectation that the cost of developing and making a drug product available in the United States for treatment of the disease or condition will be recovered from sales of the product. A company must request orphan drug designation before submitting an NDA for the drug and rare disease or condition. 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 goal dates under the Prescription Drug User Fee Act, or PDUFA, 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 indication for seven years, except in certain limited circumstances. Orphan exclusivity does not block the approval of a different drug for the same rare disease or condition, nor does it block the approval of the same drug for different indications. 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 exclusivity will not bar approval of another product under certain circumstances, including if a subsequent product with the same drug for the same indication 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.

Patent Term Restoration and Extension

A patent claiming a new drug product may be eligible for a limited patent term extension, also known as patent term restoration, 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. Patent term extension is generally available only for drug products whose active ingredient has not previously been approved by the FDA. The restoration period granted is typically one-half the time between the effective date of an IND and the submission date of an NDA, plus the time between the submission date of an NDA and the ultimate approval date. Patent term extension 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 drug 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 drugs for which approval is sought can only be extended in connection with one of the approvals. The United States PTO reviews and approves the application for any patent term extension 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 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 the 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.

Review and Approval of Drugs in Europe and Other Foreign Jurisdictions

In addition to regulations in the United States, a manufacturer is subject to a variety of regulations in foreign jurisdictions to the extent they choose to sell any drug products in those foreign countries. Even if a manufacturer obtains FDA approval of a product, it must still obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. For other countries

outside of the European Union, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary.

Clinical Trial Approval in the European Union

Pursuant to the currently applicable Clinical Trials Directive 2001/20/EC and the Directive 2005/28/EC on Good Clinical Practice, an applicant must obtain the approval from the competent national authority of the EU Member State 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. In April 2014, the European Union adopted a new Clinical Trials Regulation (EU) No 536/2014, which is set to replace the current Clinical Trials Directive 2001/20/EC. The new Clinical Trials Regulation, which will become applicable in October 2018, will overhaul the current system of approvals for clinical trials in the European Union, and it intended to simplify and streamline the approval of clinical trials in the European Union. Under the new coordinated procedure for the approval of clinical trials, the sponsor of a clinical trial will be required to submit a single application for approval of a clinical trial to a reporting EU Member State, or RMS, through an EU Portal. The new Regulation also aims to streamline and simplify the rules on safety reporting for clinical trials.

Marketing Authorization and Exclusivity

In the European Union, marketing authorizations for medicinal products may be obtained through different procedures founded on the same basic regulatory process. The centralized procedure provides for the grant of a single marketing authorization that is valid for all EU Member States. The centralized procedure is compulsory for medicinal products produced by certain biotechnological processes, products designated as orphan medicinal products, and products with a new active substance indicated for the treatment of certain diseases. On the other hand, a decentralized procedure provides for approval by one or more other concerned EU Member States of an assessment of an application for marketing authorization conducted by one EU Member State, known as the reference EU Member State. In accordance with the mutual recognition procedure, the sponsor applies for national marketing authorization in one EU Member State. Upon receipt of this authorization the sponsor can then seek the recognition of this authorization by other EU Member States.

A marketing authorization is valid for five years, in principle, and it may be renewed after five years on the basis of a reevaluation of the risk-benefit balance by the EMA or by the competent authority of the relevant EU Member State. Once renewed, the marketing authorization is valid for an unlimited period, unless the European Commission or the relevant competent authority of the EU Member State decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal period. Any marketing authorization that is not followed by the marketing of the medicinal product on the EU market (in the case of the centralized procedure) or on the market of the EU Member State which delivered the marketing authorization within three years after authorization ceases to be valid.

In the European Union, innovative medicinal products authorized in the European Union on the basis of a full marketing authorization are entitled to eight years of data exclusivity. During this period, applicants for authorization of generics of these innovative products cannot rely on data contained in the marketing authorization dossier submitted for the innovative medicinal product. Innovative medicinal products are also entitled to ten years' market exclusivity. During this ten year period no generic of this medicinal product can be placed on the EU market. The overall ten-year period will be extended to a maximum of eleven 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 authorization, is held to bring a significant clinical benefit in comparison with existing therapies.

Regulatory Requirements after Marketing Authorization

As in the U.S., both marketing authorization holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA and the competent authorities of the individual EU Member States both before and after grant of the manufacturing and marketing authorizations. The holder of an EU marketing authorization for a medicinal product must, for example, comply with EU pharmacovigilance legislation and its related regulations and guidelines which entail many requirements for conducting pharmacovigilance, or the assessment and monitoring of the safety of medicinal products. The manufacturing process for medicinal products in the European Union is also highly regulated and regulators may shut down manufacturing facilities that they believe do not comply with regulations. Manufacturing requires a manufacturing authorization, and the manufacturing authorization holder must comply with

various requirements set out in the applicable EU laws, including compliance with EU cGMP standards when manufacturing medicinal products and active pharmaceutical ingredients.

In the European Union, the advertising and promotion of approved products are subject to EU Member States' laws governing promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. In addition, other legislation adopted by individual EU Member States may apply to the advertising and promotion of medicinal products. These laws require that promotional materials and advertising in relation to medicinal products comply with the product's Summary of Product Characteristics, or SmPC, as approved by the competent authorities. Promotion of a medicinal product that does not comply with the SmPC is considered to constitute off-label promotion, which is prohibited in the European Union.

Orphan Drug Designation and Exclusivity in the European Union

Under the relevant EU Regulations, a product can be designated as an orphan medicinal product 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 European Union when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the European Union and that without incentives the medicinal product is unlikely to be developed. 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 European Union or, if such method exists, the medicinal product 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, along with a range of other benefits. Marketing authorization may also be granted, however, 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.

Regulation 847/2000 sets out criteria and procedures governing designation of orphan drugs in the European Union. Specifically, an application for designation as an orphan product can be made any time prior to the filing of an application for approval to market the product. While marketing authorization for an orphan drug leads to a ten-year period of market exclusivity, that period may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan drug designation, for example because the product is sufficiently profitable not to justify market exclusivity. Market exclusivity can be revoked only in very selected cases, such as consent from the marketing authorization holder, inability to supply sufficient quantities of the product, demonstration of "clinically relevant superiority" by a similar medicinal product, or, after a review by the Committee for Orphan Medicinal Products, requested by a member state in the fifth year of the marketing exclusivity period (if the designation criteria are believed to no longer apply). Medicinal products designated as orphan drugs pursuant to Regulation 141/2000 shall be eligible for incentives made available by the European Community and by the member states to support research into, and the development and availability of, orphan drugs.

Brexit and the Regulatory Framework in the United Kingdom

On June 23, 2016, the electorate in the United Kingdom, or U.K. voted in favor of leaving the European Union in a referendum commonly referred to as "Brexit". The withdrawal of the U.K. from the European Union will take effect either on the effective date of the withdrawal agreement or, in the absence of agreement, two years after the U.K. provides a notice of withdrawal pursuant to the E.U. Treaty. The U.K. Prime Minister has stated that notice of withdrawal will be given by the end of March 2017. Since the regulatory framework for pharmaceutical products in the U.K. covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from European Union directives and regulations, Brexit could materially impact the future regulatory regime which applies to products and the approval of product candidates in the U.K. It remains to be seen how, if at all, Brexit will impact regulatory requirements for product candidates and products in the U.K.

Pharmaceutical Coverage, Pricing and Reimbursement

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 healthcare costs. Patients are unlikely to use our products unless coverage is provided and reimbursement is

adequate to cover at least a significant portion of the cost of our products. Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other foreign government authorities. Even if our product candidate is approved, sales of our products 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, such products. 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 our product candidate could reduce physician utilization and/or patient acceptance of our products once approved and have a material adverse effect on our 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 drug 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. Third-party reimbursement and coverage may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

The containment of healthcare costs also has become a priority of federal, state and foreign governments and the prices of drugs 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.

Outside the United States, ensuring adequate coverage and payment for our product candidate will face challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory marketing approval for a product and may require us to conduct a clinical trial that compares the cost effectiveness of our product candidate or products to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in our commercialization efforts.

In the European Union, 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 drug candidate to currently available therapies or so called health technology assessments, in order to obtain reimbursement or pricing approval. For example, the European Union 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. European Union 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 European Union have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage healthcare expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the European Union. The downward pressure on health care costs in general, particularly prescription drugs, 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 European Union 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 of our products, if approved in those countries.

Healthcare Law and Regulation

Healthcare 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, reporting of payments to physicians and teaching physicians and patient data privacy and security laws and regulations and other healthcare laws and regulations that may constrain our business and/or financial arrangements. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the United States 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 healthcare 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 healthcare benefit program or making false statements relating to healthcare matters;

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

- 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 collectively the Affordable Care Act, which 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 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 healthcare items or services that are reimbursed by non-governmental third-party payors, including private insurers.

Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to certain 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.

The U.S. Foreign Corrupt Practices Act, or FCPA, prohibits U.S. corporations and individuals from engaging in certain activities to obtain or retain business abroad or to influence a person working in an official capacity. It is illegal

to pay, offer to pay or authorize the payment of anything of value to any foreign government official, government staff member, political party or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity. The scope of the FCPA includes interactions with certain healthcare professionals in many countries. Equivalent laws have been adopted in other foreign countries that impose similar obligations.

Healthcare Reform

A primary trend in the United States healthcare industry and elsewhere is cost containment. 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 other medical products, government control and other changes to the healthcare system in the United States.

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

- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, although this fee would not apply to sales of certain products approved exclusively for orphan indications;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program by increasing the minimum rebate for both branded and generic drugs and revising the definition of "average manufacturer price," or AMP, for calculating and reporting Medicaid drug rebates on outpatient prescription drug prices and extending rebate liability to prescriptions for individuals enrolled in Medicare Advantage plans;
- 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 the types of entities eligible for the 340B drug discount program;
- establishment of the Medicare Part D coverage gap discount program by requiring manufacturers to provide a 50% point-of-sale-discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- the Independent Payment Advisory Board, or IPAB, which has authority to recommend certain changes to the Medicare program to reduce expenditures by the program that could result in reduced payments for prescription drugs. The IPAB implementation has been not been clearly defined, however. The Affordable Care Act provided that under certain circumstances, IPAB recommendations will become law unless Congress enacts legislation that will achieve the same or greater Medicare cost savings; and
- establishment of the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending. Funding has been allocated to support the mission of the Center for Medicare and Medicaid Innovation from 2011 to 2019.

Other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. For example, in August 2011, the Budget Control Act of 2011, among other things, created measures for

spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for fiscal years 2012 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of up to 2% per fiscal year, which went into effect in April 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2025 unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Further, recently there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed drug products. For example, there have been several recent U.S. Congressional inquiries and proposed bills designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products.

With the new Administration and Congress, there will likely be additional legislative changes, including repeal and replacement of certain provisions of the ACA. In January 2017, Congress voted to adopt a budget resolution for fiscal year 2017, or the Budget Resolution, that authorizes the implementation of legislation that would repeal portions of the ACA. The Budget Resolution is not a law, however, it is widely viewed as the first step toward the passage of legislation that would repeal certain aspects of the ACA. Further, on January 20, 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.

The President and congressional leaders have expressed interest in repealing certain ACA provisions and replacing them with alternatives that may be less costly and provide state Medicaid programs and private health plans more flexibility. It is possible that these 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. The scope of potential future legislation to repeal and replace ACA provisions is highly uncertain in many respects, and it is 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. However, at this time the coverage expansion provisions of the ACA appear most likely to be repealed and replaced.

Employees

As of December 31, 2016, we had 55 full-time employees, including 26 employees with M.D. or Ph.D. degrees. Of these full-time employees, 41 employees are engaged in research and development activities and 14 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 $13.4 million, $29.8 million and $47.7 million for the years ended December 31, 2014, 2015 and 2016, respectively. As of December 31, 2016, we had an accumulated deficit of $101.3 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 private placements of our preferred stock and our initial public offering. 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' (deficit) equity and working capital.

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

- continue the planned clinical development activities with respect to SY-1425, including a Phase 2 clinical trial for which enrollment began in the third quarter of 2016;
- continue to develop SY-1365, including initiating a Phase 1 clinical trial in the second quarter of 2017;
- 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 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, such as clinical, quality control and scientific personnel;
- add operational, financial and management information systems and personnel, including personnel to support our product development 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 successfully conduct or complete clinical trials, 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 Phase 2 clinical trial of SY-1425, and 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 development of SY-1365, 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. 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 preclinical programs. In addition, while we may seek one or more collaborators for future development of our current product candidate 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 and cash equivalents 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. 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, 2016 will enable us to fund our operating expenses and capital expenditure requirements into mid-2018. Our estimate as to how long we expect our existing cash and cash equivalents 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;
- our ability to enter into and the terms and timing of any collaborations, licensing agreements or other arrangements;
- 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.

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, 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 drug 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 clinical trials 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 the safety or efficacy of any of our product candidates in clinical trials.

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:

- 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:

- initiation and successful enrollment and completion of clinical trials;
- a safety, tolerability and efficacy profile 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 the TMRC license agreement;
- 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 future 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 genomically defined subsets of patients with relapsed or refractory acute myeloid leukemia and relapsed high-risk myelodysplastic syndrome. We anticipate having an initial data readout from the trial in the fall of 2017, which is approximately twelve months after the first patient was enrolled in the trial. We are collaborating with a third party with respect to the clinical trial assay being used to select patients with our RARA biomarker or another RARA pathway biomarker for inclusion in the trial. Our anticipated time to data in the 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 we have no previous experience recruiting patients with these biomarkers for a clinical trial. Moreover, because we have not previously conducted a clinical trial of SY-1425 in genomically defined subsets of patients or conducted a clinical trial using the clinical trial assay developed by our collaborator, our assumptions concerning the sensitivity or specificity of the assay, enrollment of patients, or the efficacy of SY-1425 in any subset of patients may

prove to be incorrect. As a result, there can be no assurance that we will enroll or have data from the trial when we anticipate.

Clinical testing is expensive, is difficult to design and implement, can take many years to complete and is inherently uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. The clinical development of our product candidates is susceptible to the risk of failure inherent at any stage of product development, including failure to demonstrate efficacy in a clinical trial or across a broad population of patients, the occurrence of adverse events that are severe or medically or commercially unacceptable, failure to comply with protocols or applicable regulatory requirements and determination by the FDA or any comparable foreign regulatory authority that a product candidate may not continue development or is not approvable. For example, a Phase 2 clinical trial of tamibarotene (the active pharmaceutical ingredient of SY-1425) for the treatment of late-stage non-small cell lung cancer, or NSCLC, under a previous license between TMRC and a third party, was terminated when interim data suggested that the 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 NSCLC patient population. Although we have no current plans to conduct studies of SY-1425 in NSCLC or combine tamibarotene with paclitaxel and carboplatin in late-stage NSCLC patients, we face a similar risk of failure in our planned clinical trials of SY-1425. It is possible that even if one or more of our product candidates has a beneficial effect, that effect will not be detected during clinical evaluation as a result of one or more of a variety of factors, including the size, duration, design, measurements, conduct or analysis of our clinical trials. Conversely, as a result of the same factors, our clinical trials may indicate an apparent positive effect of a product candidate that is greater than the actual positive effect, if any. Similarly, in our clinical trials we may fail to detect toxicity of or intolerability caused by our product candidates, or mistakenly believe that our product candidates are toxic or not well tolerated when that is not in fact the case.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us, or any 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 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 or ATRA, Retin-A, retinol (found in over-the-counter skin creams), isotretinoin and bexarotene. We have not yet tested SY-1365 in humans so the safety profile that SY-1365 will demonstrate in human clinical trials is unknown. 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. Our inability to enroll a sufficient number of genomically defined patients for our clinical trials would result in significant delays and could require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, which would cause the value of our company to decline and limit our ability to obtain additional financing. Further, if we are unable to include a sufficient number of genomically defined patients in our trials, this could compromise our ability to seek participation in the FDA's expedited review and approval programs, including Breakthrough Therapy designation and Fast Track designation, or otherwise to seek to accelerate clinical development and regulatory timelines.

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.

We have not conducted any clinical trials, and all our data results 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 occurs, 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, such as the use of chemotherapy followed by stem cell transplantation in the case of AML and MDS. SY-1425 may also face competition from other drug candidates currently in clinical development for relapsed or refractory AML and MDS, including drug candidates in development from Daiichi Sankyo Company, Limited, Boehringer Ingelheim GmbH, Agios Pharmaceuticals, Inc., Novartis AG, Astellas Pharma Inc., Seattle Genetics, Inc., Celgene Corporation, Janssen Research & Development LLC, Pfizer, Inc., Karyopharm Therapeutics Inc. and Aileron Therapeutics, Inc. 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 and high-risk MDS. In addition, we are aware of two other selective cyclin-dependent kinase 7, or CDK7, inhibitor programs, that we believe are in early preclinical development. SY-1365 may face competition from these 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.

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.

We expect to seek to establish 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 collaborators for the development and commercialization of one or more of our product candidates. 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.

Any collaboration agreements that we enter into in the future may contain restrictions on our ability to enter into potential collaborations 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.

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. We have not entered into any collaborations to date. If 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 future collaborators' abilities to successfully perform the functions assigned to them in these arrangements. In addition, any future 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.

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, worldwide license under specified patents relating to modulators of Myc/Max Screen and relating to Chem-Seq; 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 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 recently issued in-licensed United States patent relating to this subject matter. We are in communication with that third party and are seeking to have them cease offering those services in light of our issued patent. If we are unsuccessful 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 and contractors 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, or IDE. 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.

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, or any future collaborators, may seek orphan drug designations for 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.

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 biologics 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.

Current and future legislation may increase the difficulty and cost for us and any future collaborators to obtain marketing approval of and commercialize 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 future 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 Affordability Reconciliation Act. We refer to this law, as so amended, as the Affordable Care Act or 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 to eligible beneficiaries during their coverage gap period, as a condition for a manufacturer's outpatient drugs to be covered under Medicare Part D;
- extension of manufacturers' Medicaid rebate liability;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- new requirements to report certain financial arrangements with physicians and teaching hospitals;
- a new requirement to annually report drug samples that manufacturers and distributors provide to physicians; and
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

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 bills designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products.

We expect that the ACA, 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.

In addition, with the new Administration and Congress, there will likely be additional legislative changes, including repeal and replacement of certain provisions of the ACA. It remains to be seen, however, precisely what the new legislation will provide, when it will be enacted and what impact it will have on the availability of healthcare and containing or lowering the cost of healthcare. Such reforms could have an adverse effect on anticipated revenue from product candidates that we may successfully develop and for which we may obtain marketing approval and may affect our overall financial condition and ability to develop or commercialize product candidates. For example, the President and congressional leaders have expressed interest in repealing certain ACA provisions and replacing them with alternatives that may be less costly and provide state Medicaid programs and private health plans more flexibility. It is possible that these 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. The scope of potential future legislation to repeal and replace ACA provisions is highly uncertain in many respects, and it is 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.

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 any 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 United States 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. 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. This is particularly true in the European Union, which is undergoing a continued severe economic crisis. 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; Kyle D. Kuvalanka, our chief operating officer; Eric R. Olson, Ph.D., our chief scientific officer; Gerald E. Quirk, Esq., our chief legal officer; and David A. Roth, M.D., our chief medical 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. For example, our Chief Strategy Officer, Jorge Conde, has informed us of his intent to transition from Syros effective March 31, 2017. In the future, we may be dependent on other members of our management, scientific and development team.

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. Furthermore, 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 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. 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 will incur increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives and corporate governance practices.

As a public company, and particularly after we are no longer an “emerging growth company,” we will incur significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of The NASDAQ Global Select Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. We expect that we will need to hire additional accounting, finance and other personnel in connection with our efforts to comply with the requirements of being a public company and our management and other personnel will need to devote a substantial amount of time towards maintaining compliance with these requirements. These requirements will increase our legal and financial compliance costs and will make some activities more time consuming and costly. For example, we expect that the rules and regulations applicable to us as a public company may make it more difficult and more expensive for us to obtain director and officer liability insurance, which could make it more difficult for us to attract and retain qualified members of our board of directors. We are currently evaluating these rules and regulations, and cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. These rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

If we fail to establish and maintain effective internal controls, we may be unable to produce timely and accurate financial statements, and we may conclude that our internal control over financial reporting is not effective, which could adversely impact our investors' confidence and our stock price.

As a private company, we had limited accounting and financial reporting personnel and other resources with which to address our internal controls and related procedures. In connection with the audit of our consolidated financial statements for the years ended December 31, 2013 and 2014, we and our independent registered public accounting firm identified material weaknesses in our internal control over financial reporting. A material weakness is a deficiency, or a combination of deficiencies, in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of our annual or interim financial statements will not be prevented or detected on a timely basis. The material weaknesses related to our controls over the classification of certain indirect and other expenses between general and administrative and research and development, and to the accounting for stock-based compensation. We also identified deficiencies related to our controls over our accounting for income taxes. The material weaknesses that we had identified were due to the lack of appropriate oversight and review procedures by accounting personnel to properly identify and evaluate certain accounting matters that resulted in errors in our financial statements.

We have implemented measures designed to improve our internal control over financial reporting to remediate these material weaknesses, including the following:

- formalizing our processes and internal control documentation and strengthening supervisory reviews by our management;
- hiring additional qualified accounting personnel and engaged financial consultants who have significant accounting and financial reporting experience, which will enable the implementation of internal controls over financial reporting and segregating duties amongst accounting personnel; and
- implementing certain accounting systems to automate manual processes, such as tracking and accounting for stock-based awards.

We cannot assure you that the measures we have taken to date, together with any measures we may take in the future, will be sufficient to avoid potential future material weaknesses. In addition, neither our management nor an independent registered public accounting firm has ever performed an evaluation of our internal control over financial reporting in accordance with the provisions of the Sarbanes-Oxley Act because no such evaluation has been required. Had we or our independent registered public accounting firm performed an evaluation of our internal control over financial reporting in accordance with the provisions of the Sarbanes-Oxley Act, additional material weaknesses may have been identified. If we are unable to successfully remediate any future material weaknesses in our internal control over financial reporting, the accuracy and timing of our financial reporting may be adversely affected, we may be unable to maintain compliance with securities law requirements regarding timely filing of periodic reports in addition to applicable stock exchange listing requirements, investors may lose confidence in our financial reporting, and our stock price may decline as a result. We also could become subject to investigations by NASDAQ, the Securities and Exchange Commission, or SEC, or other regulatory authorities.

As a public company, we are obligated to develop and maintain proper and effective internal controls over financial reporting. Any failure to maintain the adequacy of these internal controls may adversely affect investor confidence in our company and, as a result, the value of our common shares.

Pursuant to SOX Section 404 we will be required to furnish a report by our management on our internal control over financial reporting beginning with our second filing of an Annual Report on Form 10-K with the SEC. While we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. This assessment will need to include disclosure of any material weaknesses identified by our management in our internal control over financial reporting. Our independent registered public accounting firm will not be required to attest to the effectiveness of our internal control over financial reporting until our first annual report required to be filed with the SEC following the date we are no longer an "emerging growth company," as defined in the JOBS Act. At such time as we are required to obtain auditor attestation, if we then have a material weakness, we would receive an adverse opinion regarding our internal control over financial reporting from our independent registered accounting firm.

To achieve compliance with SOX Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. During our evaluation of our internal control, if we identify one or more material weaknesses in our internal control over financial reporting, we will be unable to assert that our internal control over financial reporting is effective. We cannot assure you that there will not be material weaknesses or significant deficiencies in our internal control over financial reporting in the future. Any failure to maintain internal control over financial reporting could severely inhibit our ability to accurately report our financial condition or results of operations. If we are unable to conclude that our internal control over financial reporting is effective, or if our independent registered public accounting firm determines we have a material weakness or significant deficiency in our internal control over financial reporting, we could lose investor confidence in the accuracy and completeness of our financial reports, the market price of our ordinary shares could decline, and we could be subject to sanctions or investigations by NASDAQ, the SEC or other regulatory authorities. Failure to remedy any material weakness in our internal control over financial reporting, or to implement or maintain other effective control systems required of public companies, could also restrict our future access to the capital markets.

A significant portion of our total outstanding shares is restricted from immediate resale but may be sold into the market in the near future, which could cause the market price of our common stock to decline significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, or the perception in the market that the holders of a large number of shares of common stock intend to sell shares, could reduce the market price of our common stock. As of December 31, 2016, we had 23,385,773 shares of common stock outstanding. The holders of a majority of the outstanding shares of our common stock have rights, subject to conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders.

As of December 31, 2016, we had registered 5,804,659 shares of common stock for potential issuance under our equity compensation plans. These shares can be freely sold in the public market upon issuance and once vested, subject to volume limitations applicable to affiliates. If additional shares are sold, or if it is perceived that they will be sold, in the public market, the trading price of our common stock could decline.

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, 2016, we had federal and state net operating loss carryforwards of $86.3 million and $85.3 million, respectively, and federal and state research and development tax credit carryforwards of $2.3 million and $1.5 million, respectively, each of which if not utilized will expire at various dates through 2036. 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.

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 substantial 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.

Our certificate of incorporation designates the state courts in the State of Delaware or, if no state court located within the State of Delaware has jurisdiction, the federal court for the District of Delaware, as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could discourage lawsuits against our company and our directors and officers.

Our certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware (or, if the Court of Chancery does not have jurisdiction, the federal district court for the District of Delaware) will be the sole and exclusive forum for any derivative action or proceeding brought on our behalf, any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or employees to our company or our stockholders, any action asserting a claim against us arising pursuant to any provision of the General Corporation Law of the State of Delaware or our certificate of incorporation or bylaws, or any action asserting a claim against us governed by the internal affairs doctrine. This exclusive forum provision may limit the ability of our stockholders to bring a claim in a judicial forum that such stockholders find favorable for disputes with us or our directors or officers, which may discourage such lawsuits against us and our directors and officers.

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 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 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

Holders of Our Common Stock

As of February 28, 2017, there were approximately 55 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

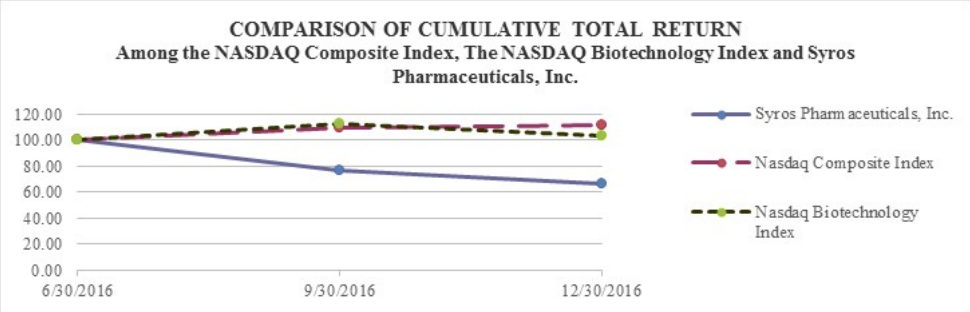
We have never declared nor paid cash dividends on our common stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. We do not intend to pay cash dividends in respect of our common stock in the foreseeable future. Any future determination 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 30, 2016, 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, 2016, we estimate that we have used approximately $25.1 million of our existing cash and cash equivalents at the time of the IPO, together with 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. We have invested the unused proceeds from the offering in marketable securities and money market accounts. There has been no material change in our planned use of the net proceeds from our IPO as described in our final prospectus filed with the SEC pursuant to Rule 424(b)(4) on June 30, 2016.

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" section of this Annual Report on Form 10-K. We have derived the consolidated statement of operations data for the years ended December 31, 2016, 2015 and 2014 and the consolidated balance sheet data as of December 31, 2016 and 2015 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 year ended December 31, 2013, and consolidated balance sheet data as of December 31, 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			
	2016	2015	2014	2013
	(in thousands, except for per share data)			
Statements of operations data:				
Revenue	$ 317	$ 317	$ —	$ —
Operating expenses:				
Research and development	37,817	24,408	10,923	6,266
General and administrative	10,463	5,729	2,512	2,367
Total operating expenses	48,280	30,137	13,435	8,633
Loss from operations	(47,963)	(29,820)	(13,435)	(8,633)
Other income (expense), net	220	2	4	(32)
Net loss	$ (47,743)	$ (29,818)	$ (13,431)	$ (8,665)
Net loss per share applicable to common stockholders - basic and diluted (1)	$ (4.05)	$ (17.55)	$ (10.26)	$ (7.57)
Weighted-average number of common shares used in net loss per share applicable to common stockholders - basic and diluted (1)	12,696,414	1,980,286	1,525,018	1,144,583

(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.

	December 31, 2016	December 31, 2015	December 31, 2014
	(in thousands)		
Balance sheet data:			
Cash, cash equivalents and marketable securities	$ 83,593	$ 35,909	$ 60,393
Working capital (1)	75,941	28,493	59,291
Total assets	91,323	43,631	61,494
Convertible preferred stock (2)	—	82,013	82,013
Total stockholders' (deficit) equity	80,602	(47,964)	(21,772)

(1) 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.
(2) 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 disease-driving 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 and drug novel targets linked to genomically defined patient populations. 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. By focusing on genomically defined subsets of patients, we believe we can conduct efficient clinical trials with a higher likelihood of success. We are currently focused on developing treatments for cancer and immune-mediated diseases and are building a pipeline of gene control medicines.

In September 2016, we began enrolling patients in a Phase 2 clinical trial for our lead product candidate, SY-1425 (tamibarotene), an oral, potent and selective retinoic acid receptor alpha, or RARα, agonist, in genomically defined subsets of patients with relapsed or refractory acute myelogenous leukemia, or AML, and relapsed high-risk myelodysplastic syndrome, or MDS. In the fourth quarter of 2016, an investigational device exemption for the assay being used to select patients for this trial was approved by the U.S. Food and Drug Administration. With this approval, we have expanded this trial to include newly diagnosed AML patients who are at least 60 years old and are not suitable candidates for standard chemotherapy, and lower-risk, transfusion-dependent MDS patients. During 2017, we intend to further expand this trial to explore the safety and efficacy of SY-1425 when combined with azacitidine, a hypomethylating agent that is commonly used to treat AML, in newly diagnosed AML patients who are at least 60 years old and not suitable candidates for standard chemotherapy. We also plan to initiate a Phase 1 clinical trial for our development candidate SY-1365, a highly potent and selective small molecule inhibitor of cyclin-dependent kinase 7, or CDK7, in patients with advanced solid tumors in the second quarter of 2017. Both of these programs may have potential in additional disease indications. Using our platform, we are also generating a pipeline of novel preclinical drug candidates in cancer, including immuno-oncology, and advancing our research efforts in rare cancers and in autoimmune and rare genetic diseases. We plan to advance one of our four preclinical programs to support a potential investigational new drug application, or IND, filing in 2019. Our goal is to build a fully integrated biopharmaceutical company based on our leadership position in gene control.

Since our inception in November 2011, we have devoted substantially all of our resources to organizing and staffing our company, business planning, raising capital, developing our technology platform and conducting preclinical research for our product candidates. We do not have any products approved for sale and have not generated any revenue from product sales. We have financed our operations to date primarily through private placements of preferred stock and the initial public offering of our common stock, or IPO. From inception through December 31, 2016, we raised an aggregate of $122.2 million of gross proceeds from sales of our preferred stock and from the issuance of convertible notes that subsequently converted to preferred stock to fund operations. On July 6, 2016, we completed the IPO, pursuant to which we issued and sold 4,600,000 shares of our common stock (inclusive of 600,000 shares of common stock sold by us pursuant to the full exercise of an option to purchase additional shares granted to the underwriters in connection with the offering) at a price to the public of $12.50 per share, resulting in gross proceeds of $57.5 million. We received approximately $49.9 million in net proceeds, after deducting underwriting discounts and commissions and offering costs of approximately $7.6 million. Our common stock began trading on the NASDAQ Global Select Market on June 30, 2016. Upon the closing of the IPO, all outstanding shares of our convertible preferred stock converted into 15,988,800 shares of common stock and no shares of our convertible preferred stock are currently outstanding.

Since inception, we have incurred significant operating losses. Our net losses were $47.7 million, $29.8 million, and $13.4 million for the years ended December 31, 2016, 2015 and 2014, respectively. As of December 31, 2016, we had an accumulated deficit of $101.3 million. We expect to continue to incur significant expenses and operating losses for the foreseeable future. We anticipate that our expenses will increase significantly in connection with our ongoing activities if and as we:

- continue the planned clinical development activities with respect to SY-1425, including a Phase 2 clinical trial for which enrollment began in September 2016;
- continue to develop SY-1365, including initiating a Phase 1 clinical trial in the second quarter of 2017;

- 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 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, such as clinical, quality control and scientific personnel;
- add operational, financial and management information systems and personnel, including personnel to support our product development and help us comply with our obligations as a public company; and
- add equipment and physical infrastructure to support our research and development programs.

Because of the numerous risks and uncertainties associated with product development, we are unable to predict the timing or amount of increased expenses or when or if we will be able to achieve or maintain profitability. Even if we are able to generate product sales, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

Financial Operations Overview

Revenue

To date, we have not generated any revenue from product sales and do not expect to generate any revenue from product sales for the foreseeable future. For additional information about our revenue recognition policy, see the section captioned “Critical Accounting Policies and Estimates – Revenue” below.

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.

The following summarizes our most advanced current research and development programs:

- Our lead product candidate, SY-1425, is an oral, potent and selective RARα agonist. We began enrolling patients in a Phase 2 clinical trial in genomically defined subsets of patients with relapsed or refractory AML and relapsed high-risk MDS in September 2016. In the fourth quarter of 2016, an investigational device exemption for the assay being used to select patients for this trial was approved by the U.S. Food and Drug Administration, or FDA. With this approval, we expanded this trial to include newly diagnosed AML patients who are at least 60 years old who are not suitable candidates for standard chemotherapy, and lower-risk, transfusion-dependent MDS patients.
- Our development candidate SY-1365 is a highly potent and selective small molecule inhibitor of CDK7. We expect to initiate a Phase 1 clinical trial in patients with advanced solid tumors in the second quarter of 2017.

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.

We have not provided program costs for the year ended December 31, 2014 because prior to 2015, we did not track or record our research and development expenses on a program-by-program basis. The following table summarizes our external research and development expenses by program, as well as expenses not allocated to programs, for the years ended December 31, 2016 and 2015 (amounts in thousands):

	Year Ended December 31,	
	2016	2015
SY-1365 and other CDK7 program external costs	$ 8,129	$ 6,998
SY-1425 external costs	7,940	1,484
Other research and platform programs external costs	7,184	6,239
Employee-related expenses, including stock-based compensation	11,214	8,077
Facilities and other expenses	3,350	1,610
Total research and development expenses	$ 37,817	$ 24,408

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 and remediate the material weakness in our internal control over financial reporting. We also anticipate that we will incur increased accounting, audit, legal, regulatory, compliance and director and officer insurance costs, as well as investor and public relations expenses, associated with operating as a public company.

Other Income (Expense), Net

Other income (expense), 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 prospectus, 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 contains a single unit of accounting and we recognize 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 is 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.

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

	Year Ended December 31,		
	2016	2015	2014
Weighted-average risk-free interest rate	1.36 %	1.78 %	2.00 %
Expected dividend yield	— %	— %	— %
Expected option term	5.98	6.09	7.03
Volatility	85.39 %	82.71 %	85.51 %

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, 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 (amounts in thousands):

	Year Ended December 31,			
	2016	2015	Dollar Change	% 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 are responsible for the conduct of all activities under separate projects, as defined in the research agreement. We recognize 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 (amounts 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 clinical and 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, including a $1.0 million milestone payment made under our license agreement with TMRC Co., Ltd., which we refer to as the TMRC license agreement, 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 rent, 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 following table summarizes our general and administrative expenses for the years ended December 31, 2016 and 2015, together with the changes to those items in dollars (amounts in thousands):

	Year Ended December 31,			
	2016	2015	Dollar Change	% Change
Employee-related expenses, excluding stock-based compensation	$ 3,662	$ 2,145	$ 1,517	71 %
Stock-based compensation	1,254	500	754	151 %
Consulting, licensing and professional fees	3,672	2,215	1,457	66 %
Facilities and other expenses	1,875	869	1,006	116 %
Total general and administrative expenses	$10,463	$ 5,729	$ 4,734	83 %

The change in general and administrative expense was primarily attributable to the following:

- an increase of approximately $1.5 million, or 71%, for employee-related costs, including salary and benefits as a result of the increase in headcount to support growth of the Company;
- an increase of approximately $0.8 million, or 151%, for stock-based compensation expense;
- an increase of approximately $1.5 million, or 66% of consulting and professional fees associated with operating as a public company; and
- and increase of approximately $1.0 million, or 116% in facilities costs including rent, depreciation and maintenance expenses associated with our operating lease at our corporate headquarters beginning in August 2015.

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.

Comparison of Years Ended December 31, 2015 and 2014

The following table summarizes our results of operations for the years ended December 31, 2015 and 2014, together with the changes in those items in dollars (amounts in thousands):

	Year Ended December 31, 2015	2014	Dollar Change	Dollar Change
Statements of Operations Data:				
Revenue	$ 317	$ —	$ 317	100 %
Operating expenses:				
Research and development	24,408	10,923	13,485	123 %
General and administrative	5,729	2,512	3,217	128 %
Total operating expenses	30,137	13,435	16,702	124 %
Other income, net	2	4	(2)	(50)%
Net loss	$ (29,818)	$ (13,431)	$ 16,387	122 %

Revenue

Under our research agreement, we recognized revenue of $0.3 million during the year ended December 31, 2015. No revenue was recognized during the year ended December 31, 2014.

Research and Development Expense

Research and development expense increased by approximately $13.5 million, or 123%, from $10.9 million for the year ended December 31, 2014 to $24.4 million for the year ended December 31, 2015. The following table summarizes our research and development expenses for the year ended December 31, 2015 and 2014, together with the changes to those items in dollars (amounts in thousands):

	Year Ended December 31, 2015	2014	Dollar Change	% Change
External research and development	$12,749	$ 5,520	$ 7,229	131 %
Employee-related expenses, excluding stock-based compensation	5,344	2,984	2,360	79 %
Stock-based compensation	2,733	830	1,903	229 %
Consulting, licensing and professional fees	1,972	682	1,290	189 %
Facilities and other expenses	1,610	907	703	78 %
Total research and development expenses	$24,408	$10,923	$ 13,485	123 %

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 $7.2 million, or 131% for costs from third parties that conduct research and development and preclinical activities on our behalf, including approximately $2.6 million in chemistry expenses for contract chemistry personnel and increased chemistry analysis and $1.2 million for *in vivo* study costs to support advancement of our growing pipeline;
- an increase of approximately $2.4 million, or 79% for increased personnel related expenses, including increased salary and benefits primarily due to the hire of research and development personnel;
- an increase of approximately $1.9 million, or 229% for increased stock-based compensation expense;
- an increase of approximately $1.3 million, or 189% in consulting, licensing, and professional fees, due to the $0.5 million upfront payment made under the TMRC license agreement in September 2015; and

- an increase of approximately $0.7 million, or 78% for increases in facilities costs including rent, depreciation and maintenance expenses associated with our operating lease.

General and Administrative Expense

General and administrative expense increased by approximately $3.2 million, or 128% from $2.5 million for the year ended December 31, 2014 to $5.7 million for the year ended December 31, 2015. The following table summarizes our general and administrative expenses for the years ended December 31, 2015 and 2014, together with the changes to those items in dollars (amounts in thousands):

	Year Ended December 31,			
	2015	2014	Dollar Change	% Change
Employee-related expenses, excluding stock-based compensation	$ 2,145	$ 914	$ 1,231	135 %
Stock-based compensation	500	107	393	367 %
Consulting, licensing and professional fees	2,215	1,341	874	65 %
Facilities and other expenses	869	150	719	479 %
Total general and administrative expenses	$ 5,729	$ 2,512	$ 3,217	128 %

The change in general and administrative expense was primarily attributable to the following:

- an increase of approximately $1.2 million, or 135% for employee-related costs, including salary and benefits as a result of the increase in administrative function headcount;
- an increase of approximately $0.4 million, or 367% for stock-based compensation expense;
- an increase of approximately $0.9 million, or 65% primarily for consulting 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; and
- increase of approximately $0.7 million, or 479% in facilities costs including rent, depreciation and maintenance expenses associated with our operating lease.

Other Income, Net

Other income, net consists of interest income on our cash and cash equivalents offset by interest expense related to our equipment financing arrangement. The decrease in other income from the year ended December 31, 2014 to the year ended December 31, 2015 is due to higher interest expense related to our equipment financing arrangement entered into in 2015.

Liquidity and Capital Resources

Sources of Liquidity

We funded our operations from inception through December 31, 2016 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, and $49.9 million in net proceeds from the sale of common stock in the IPO.

As of December 31, 2016, we had cash, cash equivalents and marketable securities of approximately $83.6 million.

Cash Flows

The following table provides information regarding our cash flows for the years ended December 31, 2016, 2015 and 2014 (in thousands):

	Year Ended December 31,		
	2016	2015	2014
Net cash provided by (used in):			
Operating activities	$(40,536)	$(23,030)	$(11,969)
Investing activities	(27,342)	(1,176)	(201)
Financing activities	90,557	(278)	68,762
Net increase (decrease) in cash and cash equivalents	$ 22,679	$(24,484)	$ 56,592

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 $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 our 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 operating activities was $23.0 million during the year ended December 31, 2015 compared to $12.0 million during the year ended December 31, 2014. The increase in cash used in operating activities was primarily due to an increase in net loss of $16.4 million for the year ended December 31, 2015 as compared to the year ended December 31, 2014.

Net Cash Used in Investing Activities

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 used in investing activities was $1.2 million during the year ended December 31, 2015 compared to $0.2 million during the year ended December 31, 2014. The increase in cash used in investing activities was due to increased purchases of property and equipment.

Net Cash Provided by (Used in) Financing Activities

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.

Net cash used in financing activities was $0.3 million during the year ended December 31, 2015 compared to net cash provided by financing activities of $68.8 million during the year ended December 31, 2014. The decrease in cash provided by financing activities was primarily due to the issuance of $15.8 million of Series A-3 preferred stock and $53.1 million of Series B preferred stock druing the year ended December 31, 2014, with no preferred stock issuance occurring during the year ended December 31, 2015.

Funding Requirements

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue and expand clinical trials of SY-1425, advance the development of 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 drug candidates.

On July 6, 2016, we completed our IPO, in which we issued and sold 4,600,000 shares of 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. We received approximately $49.9 million in net proceeds after deducting underwriting discounts and commissions and offering costs of $7.6 million. We believe that our cash, cash equivalents and marketable securities as of December 31, 2016 will enable us to fund our operating expenses and capital expenditure requirements into mid-2018. 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;
- 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, your

ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. 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

The following table summarizes our significant contractual obligations as of payment due date by period at December 31, 2016:

	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 (1)	$ 232	$ 177	$ 53	$ 2	$ —
Operating lease payments (2)	4,995	1,252	2,613	1,130	—
Total	$ 5,227	$ 1,429	$ 2,666	$ 1,132	$ —

(1) We have a capital lease for laboratory equipment that expires in March 2018.
(2) We lease office space at 620 Memorial Drive in Cambridge, Massachusetts under a non-cancellable operating lease that expires in October 2020.

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. No payments were made under this supply management arrangement during the year ended December 31, 2015.

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, 2016, 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, 2016.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

SYROS PHARMACEUTICALS, INC.

INDEX TO FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

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

We have audited the accompanying consolidated balance sheets of Syros Pharmaceuticals, Inc. as of December 31, 2016 and 2015, and the related consolidated statements of operations, comprehensive loss, convertible preferred stock and stockholders' (deficit) equity and cash flows for each of the three years in the period ended December 31, 2016. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. We were not engaged to perform an audit of the Company's internal control over financial reporting. Our audits included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, 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. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of Syros Pharmaceuticals, Inc. at December 31, 2016 and 2015, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2016, in conformity with U.S. generally accepted accounting principles.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 20, 2017

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

	December 31, 2016	December 31, 2015
Assets		
Current assets:		
Cash and cash equivalents	$ 58,588	$ 35,909
Marketable securities	25,005	—
Accounts receivable	867	—
Prepaid expenses and other current assets	1,048	540
Total current assets	85,508	36,449
Property and equipment, net	4,850	4,799
Other long-term assets	482	1,900
Restricted cash	483	483
Total assets	$ 91,323	$ 43,631
Liabilities, convertible preferred stock and stockholders' equity (deficit)		
Current liabilities:		
Accounts payable	$ 2,415	$ 5,035
Accrued expenses	6,115	2,504
Deferred revenue	550	—
Deferred rent, current portion	319	284
Capital lease obligations, current portion	168	133
Total current liabilities	9,567	7,956
Deferred rent, net of current portion	1,101	1,420
Capital lease obligations, net of current portion	53	206
Commitments and contingencies (Note 9)		
Series A convertible preferred stock, $0.001 par value; 0 and 30,350,000 shares authorized, issued and outstanding at December 31, 2016 and December 31, 2015, respectively	—	29,015
Series B convertible preferred stock, $0.001 par value; 0 and 16,893,931 shares authorized, issued and outstanding at December 31, 2016 and December 31, 2015, respectively	—	52,998
Stockholders' equity (deficit) :		
Preferred stock, $0.001 par value; 10,000,000 and 0 shares authorized at December 31, 2016 and 2015, respectively, 0 shares issued and outstanding at December 31, 2016 and 2015 , respectively	—	—
Common stock, $0.001 par value; 200,000,000 and 66,171,908 shares authorized at December 31, 2016 and 2015, respectively; 23,380,888 and 2,363,018 shares issued and outstanding at December 31, 2016 and 2015, respectively	23	2
Additional paid-in capital	181,844	5,547
Accumulated other comprehensive loss	(9)	—
Accumulated deficit	(101,256)	(53,513)
Total stockholders' equity (deficit)	80,602	(47,964)
Total liabilities, convertible preferred stock and stockholders' equity (deficit)	$ 91,323	$ 43,631

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,		
	2016	2015	2014
Revenue	$ 317	$ 317	$ —
Operating expenses:			
Research and development	37,817	24,408	10,923
General and administrative	10,463	5,729	2,512
Total operating expenses	48,280	30,137	13,435
Loss from operations	(47,963)	(29,820)	(13,435)
Other income, net	220	2	4
Net loss	$ (47,743)	$ (29,818)	$ (13,431)
Accrued dividends on preferred stock	(3,681)	(4,934)	(2,211)
Net loss applicable to common stockholders	$ (51,424)	$ (34,752)	$ (15,642)
Net loss per share applicable to common stockholders - basic and diluted	$ (4.05)	$ (17.55)	$ (10.26)
Weighted-average number of common shares used in net loss per share applicable to common stockholders - basic and diluted	12,696,414	1,980,286	1,525,018

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,		
	2016	2015	2014
Net loss	$ (47,743)	$ (29,818)	$ (13,431)
Other comprehensive loss:			
Unrealized holding losses on marketable securities	(9)	—	—
Comprehensive loss	$ (47,752)	$ (29,818)	$ (13,431)

See accompanying notes to consolidated financial statements.

SYROS PHARMACEUTICALS, INC.
CONSOLIDATED STATEMENTS OF CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' (DEFICIT) EQUITY
(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, 2013	14,600,000	$ 13,266	—	$ —	1,379,669	$ 1	$ 970	$ —	$ (10,264)	$ (9,293)
Issuance of Series A convertible preferred stock, net of issuance costs of $1	15,750,000	15,749	—	—	—	—	—	—	—	—
Issuance of Series B convertible preferred stock, net of issuance costs of $152	—	—	16,893,931	52,998	—	—	—	—	—	—
Exercise of stock options and vesting of restricted stock awards	—	—	—	—	260,340	—	15	—	—	15
Stock-based compensation expense	—	—	—	—	—	—	937	—	—	937
Net loss	—	—	—	—	—	—	—	—	(13,431)	(13,431)
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

See accompanying notes to consolidated financial statements.

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

	Year ended December 31,		
	2016	2015	2014
Operating activities			
Net loss	$ (47,743)	$ (29,818)	$ (13,431)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	1,273	602	258
Loss on disposal of assets	4	17	—
Stock-based compensation expense	4,234	3,233	937
			—
Net amortization of premiums and discounts on marketable securities	6	—	—
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(508)	(390)	(38)
Accounts receivable	(317)	—	—
Other long-term assets	(482)	—	—
Restricted cash	—	(413)	—
Accounts payable	(404)	2,022	334
Accrued expenses	3,685	1,663	7
Deferred rent and lease incentive	(284)	54	(36)
Net cash used in operating activities	(40,536)	(23,030)	(11,969)
Investing activities			
Purchases of property and equipment	(2,322)	(1,176)	(201)
Purchases of marketable securities	(25,020)	—	—
Net cash used in investing activities	(27,342)	(1,176)	(201)
Financing activities			
Payments on capital lease obligations	(135)	(50)	—
Proceeds from issuance of convertible preferred stock, net of issuance costs	39,813	—	68,747
Proceeds from issuance of common stock	395	392	15
Proceeds from initial public offering of common stock, net of commissions and underwriting discounts	53,480	—	—
Payments of offering costs	(2,996)	(620)	—
Net cash provided by (used in) financing activities	90,557	(278)	68,762
Increase (decrease) in cash and cash equivalents	22,679	(24,484)	56,592
Cash and cash equivalents			
Beginning of period	35,909	60,393	3,801
End of period	$ 58,588	$ 35,909	$ 60,393
Supplemental disclosure of cash flow information:			
Cash paid for interest	$ 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	$ 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	$ —	$ 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 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 drug 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 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 Fourth Amended and Restated 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 is expected to impact the year-over-year comparability of the Company's net loss per share calculations over the next year.

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 $47.7 million, $29.8 million and $13.4 million for the years ended December 31, 2016, 2015 and 2014, respectively. As of December 31, 2016, the Company had an accumulated deficit of $101.3 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 and the sale of common stock in the IPO. 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' (deficit) equity and working capital. The Company believes that its cash, cash equivalents, and marketable securities of $83.6 million as of December 31, 2016 will be sufficient to allow the Company to fund its current operating plan and capital expenditure requirements into mid-2018.

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

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

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, are stated at fair value. The Company maintains its bank accounts at one major financial institution.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

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' (deficit) equity. 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.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

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, 2016.

Other Long-Term Assets

At December 31, 2015, other long-term assets consisted of deferred issuance costs, which included direct incremental legal and accounting fees relating to the IPO, and the Company's Series B preferred stock financing that closed in January 2016. Approximately, $1.9 million of deferred issuance costs were incurred and capitalized as of December 31, 2015. 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.

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.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

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 contains 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 recognizes revenue under its research agreement based upon the completed performance method of revenue recognition as it is unable to reasonably estimate the period of performance of the services and the delivery of the final study report is 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-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 research and development in the period in which they are achieved.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

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.

The amount of stock-based compensation expense recognized during a period is based on the fair value of the portion of the awards that are ultimately expected to vest. Forfeitures are estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates. The term "forfeitures" is distinct from "cancellations" or "expirations" and represents only the unvested portion of the surrendered option. The Company evaluates its forfeiture rate at each reporting period. Ultimately, the actual expense recognized over the vesting period will be for only those options that vest.

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. For stock-based awards granted to non-employees, compensation expense is recognized over the period during which services are rendered by such 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 early adopted the provisions of ASU No. 2015-17, *Income Taxes (Topic 740): Balance Sheet Classification of Deferred Taxes* ("ASU 2015-17") on a prospective basis for the year ended December 31, 2015. The standard requires that deferred tax assets and liabilities be classified as noncurrent on the balance sheet rather than being separated into current and noncurrent.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

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,		
	2016	2015	2014
Convertible preferred stock	—	12,598,370	12,598,370
Stock options	2,543,435	2,226,698	1,330,077
Unvested restricted stock	4,885	256,881	595,541
	2,548,320	15,081,949	14,523,988

The weighted average number of common shares used in net loss per share applicable to common stockholders on a basic and diluted basis were 12,696,414, 1,980,286 and 1,525,018 for the years ended December 31, 2016, 2015 and 2014, 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. The Company currently has one revenue arrangement. In the event another revenue arrangement is executed, the Company plans to use the modified retrospective approach in adopting this standard.

In August 2014, the FASB issued ASU No. 2014-15, *Presentation of Financial Statements—Going Concern (Subtopic 205-40): Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern.* This new standard is intended to define management's responsibility to evaluate whether there is substantial doubt about an entity's ability to continue as a going concern within one year of the date of issuance of the entity's financial statements and to provide related footnote disclosures. The standard is effective for interim and annual periods ending after December 15, 2016. The standard did not have a material impact on the Company's consolidated financial statements or footnote disclosures as of the December 31, 2016 adoption date, but may require additional disclosures in future periods.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

In February 2016, the FASB issued ASU No. 2016-02, *Leases* ("ASU 2016-02"), which amends a number of aspects of lease accounting, including requiring lessees to recognize almost all leases with a term greater than one year as a right-of-use asset and corresponding liability, measured at the present value of the lease payments. ASU 2016-02 is effective for fiscal years beginning after December 15, 2018 and interim periods within those years, which is 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 lease.

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 for forfeitures as the 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. Early adoption is permitted. The Company expects to adopt ASU 2016-09 for annual reporting periods beginning after December 15, 2016, including interim reporting periods within that reporting year. The Company expects to apply ASU 2016-09 using a modified retrospective approach and adopt the option to recognize gross stock compensation expense with actual forfeitures recognized as they occur, with an immaterial cumulative-effect adjustment to retained earnings recognized as of January 1, 2017. The adoption of ASU 2016-09 also requires all income tax adjustments to be recorded in the consolidated statements of operations. The Company does not expect this adoption to have a material impact since the expected increase in net deferred tax assets will be 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 was $0.4 million.

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, 2016 and December 31, 2015 (in thousands):

Description	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

Description	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
Money market funds, included in cash equivalents	$ 35,909	$ —	$ —	$ 35,909

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

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, 2016, 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, 2016, the Company held 10 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, 2016 was $25.0 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, 2016.

4. Fair Value Measurements

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

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

Description	December 31, 2015	Active Markets (Level 1)	Observable Inputs (Level 2)	Unobservable Inputs (Level 3)
Money market funds, included in cash equivalents	$ 35,909	$35,909	$ —	$ —

5. Restricted Cash

At December 31, 2016 and December 31, 2015, 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.

6. Property and Equipment

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

	Estimated useful life (in years)	December 31, 2016	December 31, 2015
Laboratory equipment	5	$ 3,612	$ 2,676
Computer equipment	3	401	237
Furniture and fixtures	4	395	349
Leasehold improvements	Shorter of 7 years or life of lease	2,599	2,468
Construction in process		18	—
		$ 7,025	$ 5,730
Less: Accumulated depreciation		(2,175)	(931)
Total property and equipment, net		$ 4,850	$ 4,799

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

Depreciation expense, including depreciation expense for assets recorded under capital leases, for the years ended December 31, 2016, 2015 and 2014 was $1.3 million, $0.6 million and $0.3 million, respectively. Laboratory equipment included assets recorded under capital leases of $0.4 million at December 31, 2016 (Note 8). Accumulated depreciation from assets recorded under capital leases was $0.1 million at December 31, 2016.

7. Accrued Expenses

Accrued expenses consist of the following (in thousands):

	December 31, 2016	December 31, 2015
Employee compensation and benefits	$ 1,911	$ 709
External research and preclinical development	3,290	981
Professional fees	819	399
Facilities	90	414
Restricted stock liability	5	1
	$ 6,115	$ 2,504

8. Indebtedness

Equipment Financing

In March 2015, the Company entered into a lease agreement with a vendor for certain laboratory equipment. The Company financed $389,000 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, 2016, the Company made payments of $152,000, of which $18,000 related to interest. At December 31, 2016, $206,000 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, 2016:

Year	(in thousands)
2017	$ 177
2018	48
2019	5
2020	2
	$ 232

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 $882,000 for the year ended December 31, 2016 and $320,000 for the year ended December 31, 2015 related to the 2015 Lease. The 2015 Lease agreement required the Company to issue an original letter of credit in the amount of $483,000, which is included in restricted cash in the accompanying balance sheet at December 31, 2016 and December 31, 2015.

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

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

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, 2016:

Year	(in thousands)
2017	$ 1,252
2018	1,288
2019	1,325
2020	1,130
	$ 4,995

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, 2016. No future potential milestone payments have been accrued as of December 31, 2015 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 the Dana-Farber, pursuant to which the Company was granted a worldwide, sublicensable license under specified patents relating to modulators of Myc/Max Screen, relating to Chem-Seq 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, 2016 and December 31, 2015, 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 $1.0 million and $0.5 million for the year ended December 31, 2016 and 2015, respectively, for annual license maintenance fees and research services.

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 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

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

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

The Company also entered into a supply management agreement with TMRC, under which the Company agreed to pay TMRC a fee for each kilogram of SY-1425 active pharmaceutical ingredient that is produced. No payments were made under 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, 2015 or December 31, 2016.

10. Convertible Preferred Stock

On July 6, 2016, upon the closing of the IPO, all of the then-outstanding shares of the Company's convertible preferred stock automatically converted into 15,988,800 shares of common stock. The Company has 10,000,000 shares of preferred stock authorized as of December 31, 2016. The authorized preferred stock was classified as stockholders' equity at December 31, 2016.

11. Stock-Based Payments

2016 Stock Incentive Plan

The 2016 Stock Incentive Plan (the "2016 Plan") was adopted by the board of directors on December 15, 2015 and approved by the stockholders on June 17, 2016 and became effective upon the Company's closing of the IPO, or July 6, 2016. 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 Company initially reserved 3,218,742 shares of common stock for the issuance of awards under the 2016 Plan, which will be cumulatively increased on January 1 of each calendar year by the least of 6,000,000 shares of common stock, 4.0% of the outstanding shares of common stock as of such date, or such lesser amount as specified by the compensation committee of the Company's 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. At December 31, 2016, 2,669,252 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 Company's 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 one year 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 2016 ESPP initially will provide participating employees with the opportunity to purchase up to

an aggregate of 586,666 shares of the Company's common stock. 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.

Stock Options

Performance-Based Stock Options

The Company has granted stock options to management for which the vesting of such stock options 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. For the year ended December 31, 2016 and 2015, the Company recorded additional stock-based compensation expense of $0.2 million and $26,000, respectively, related to the achievement of certain performance-based milestones. As of December 31, 2016, there was $1.0 million of unrecognized stock-based compensation expense related to the performance-based stock options granted to management.

During the year ended December 31, 2016, the Company granted 75,000 stock options to an advisor for which the vesting of such stock options accelerates upon the achievement of performance-based criteria. As of December 31, 2016, no such performance-based criteria were achieved.

A summary of the status of stock options as of December 31, 2015 and December 31, 2016 and changes during the year ended December 31, 2016 is presented below:

	Shares	Weighted Average Exercise Price	Remaining Contractual Life (in years)	Aggregate Intrinsic Value (in thousands)
Outstanding at December 31, 2015	2,226,698	$ 3.83	8.8	$ 11,185
Granted	739,541	11.95		
Exercised	(250,408)	1.59		
Cancelled	(172,396)	3.48		
Outstanding at December 31, 2016	2,543,435	$ 6.44	8.3	$ 14,898
Exercisable at December 31, 2016	826,570	$ 3.06	7.4	$ 7,520
Vested and expected to vest at December 31, 2016	2,543,435	$ 6.44	8.3	$ 14,898

The intrinsic value of options exercised during the years ended December 31, 2016, 2015 and 2014 was $2.4 million, $2.0 million, and $6,000, respectively.

Cash received from option exercises during the years ended December 31, 2016, 2015, and 2014 was $0.4 million, $0.4 million, and $14,000, 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

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

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, 2015 and December 31, 2016 and changes during the year ended December 31, 2016 is presented below:

	Shares	Weighted Average Grant Date Fair Value
Unvested at December 31, 2015	256,881	$ 0.38
Vested	(178,662)	0.39
Repurchased	(73,334)	0.38
Unvested at December 31, 2016	4,885	0.98

The total fair value of restricted stock vested during the years ended December 31, 2016, 2015, and 2014 was $0.1 million, $0.1 million, and $0.1 million, respectively, based upon the number of restricted stock awards vested multiplied by the fair vale of the Company's common stock on the grant date.

Certain shares of restricted stock vest upon the achievement of specified performance objectives as well as continued service to the Company. As of December 31, 2016, management determined that certain milestones were achieved, and the Company recorded additional stock-based compensation expense of $1.0 million, related to the achievement of certain performance-based milestones.

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,		
	2016	2015	2014
Weighted-average risk-free interest rate	1.36 %	1.78 %	2.00 %
Expected dividend yield	— %	— %	— %
Expected option term	5.98	6.09	7.03
Volatility	85.39 %	82.71 %	85.51 %

The weighted-average grant date fair value per share of options granted in the years ended December 31, 2016, 2015 and 2014 was $8.58, $4.88 and $1.46, 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,		
	2016	2015	2014
Research and development	$ 2,980	$ 2,733	$ 830
General and administrative	1,254	500	107
Total stock-based compensation expense	$ 4,234	$ 3,233	$ 937

As of December 31, 2016, there was $8.8 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 3.0 years. Additionally, as of December 31, 2016, there was $0.8 million of total unrecognized compensation cost related to non-vested stock options granted to non-employees. 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.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

12. Related Party Transactions

During the year ended December 31, 2016 and 2015, the Company paid one of its stockholders $1.3 million and $3.1 million, respectively, for external research and preclinical development services. During the year ended December 31, 2015, the Company paid $0.3 million to one of its stockholders for rent and other miscellaneous facilities costs related to the Company's operating lease that expired in August 2015. No payments were made to this stockholder for the year ended December 31, 2016.

13. Income Taxes

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, 2016, 2015 and 2014:

	Year ended December 31,		
	2016	2015	2014
Federal income tax computed at federal statutory tax rate	34.00 %	34.00 %	34.00 %
State income tax, net of federal benefit	4.79	4.70	4.86
Permanent items	(2.83)	(3.33)	(1.94)
Federal and state research and development credits	2.93	2.66	4.73
Other	(0.08)	0.12	—
Change in valuation allowance	(38.81)	(38.15)	(41.65)
Effective income tax rate	0.00 %	0.00 %	0.00 %

The principal components of the Company's deferred tax assets and liabilities consist of the following at December 31, 2016 and 2015, respectively (in thousands):

	Year ended December 31,		
	2016	2015	2014
Deferred tax assets:			
Federal and state net operating loss carryforwards	$ 33,846	$ 17,569	$ 7,969
Tax credit carryforwards	3,350	1,953	1,121
Intangible assets	197	313	430
Stock-based compensation	247	186	87
Leasehold incentive	467	589	—
Other	1,605	545	83
Total deferred tax assets	39,712	21,155	9,690
Less valuation allowance	(39,624)	(21,095)	(9,690)
Net deferred tax assets	88	60	—
Deferred tax liabilities:			
Fixed assets	(88)	(60)	—
Total deferred tax liabilities	(88)	(60)	—
Net deferred taxes	$ —	$ —	$ —

As of December 31, 2016, the Company had federal net operating loss ("NOL") carryforwards of approximately $86.3 million and state net operating loss carryforwards of $85.3 million, which are available to reduce future taxable income. The Company also had federal tax credits of approximately $2.3 million and state tax credits of $1.5 million, which may be used to offset future tax liabilities. The NOL and tax credit carryforwards will expire at various dates through 2036. The NOL and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service ("IRS") 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 tax attributes 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, 2016 and 2015, 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 $18.5 million in 2016 and $11.4 million in 2015 primarily relates to the net loss incurred by the Company.

As of December 31, 2016, the Company had $1.0 million of federal and state net operating losses related to excess tax deductions that have been excluded from the above table. The benefit of these net operating losses will be recognized as an increase in additional paid in capital when it results in a reduction in taxes payable.

The Company has not yet conducted a study of its research and development credit carryforwards. This study may result in an adjustment to the Company's research and development credit carryforwards; however, until a study is completed and any adjustment is known, no amounts are being presented as an uncertain tax position. A full valuation allowance has been provided against the Company's research and development credits, and if an adjustment is required, this adjustment would be offset by an adjustment to the valuation allowance. Thus, there would be no impact to the balance sheets or statements of operations if an adjustment were required.

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. At December 31, 2016 and 2015, 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 tax examinations for the tax years ended December 31, 2013 through December 31, 2016. 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.

14. 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 determines 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 terminates automatically if the Counterparty does not notify the Company that it would like to commence the next research project.

In exchange for these research services, the Company may receive funding of up to $3.0 million over the term of the agreement. The Company will recognize 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 $0.3 million during each of the years ended December 31, 2016 and December 31, 2015 under the agreement.

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

15. 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. Through December 31, 2016, no contributions had been made to the plan by the Company.

16. Subsequent Event

TMRC Co. Ltd

In March 2017, the Company paid TMRC approximately $0.4 million for the production of SY-1425 active pharmaceutical ingredient under the supply management agreement with TMRC.

17. Selected Quarterly Financial Data (unaudited)

The following table contains selected quarterly financial information for 2016 and 2015. 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, 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

Syros Pharmaceuticals, Inc.
Notes to Consolidated Financial Statements (Continued)

	Three Months Ended			
	March 31, 2015	June 30, 2015	September 30, 2015	December 31, 2015
Revenue	$ —	$ 317	$ —	$ —
Operating expenses:				
Research and development	3,736	5,428	6,866	8,378
General and administrative	836	984	1,598	2,311
Total operating expenses	4,572	6,412	8,464	10,689
Loss from operations	(4,572)	(6,095)	(8,464)	(10,689)
Other income (expense), net	4	(2)	—	—
Net loss	$ (4,568)	$ (6,097)	$ (8,464)	$ (10,689)
Accrued dividends on preferred stock	(1,217)	(1,230)	(1,243)	(1,244)
Net loss applicable to common stockholders	$ (5,785)	$ (7,327)	$ (9,707)	$ (11,933)
Net loss per share applicable to common stockholders - basic and diluted	$ (3.44)	$ (4.16)	$ (4.51)	$ (5.14)
Weighted-average number of common shares used in net loss per share applicable to common stockholders - basic and diluted	1,682,690	1,761,457	2,150,274	2,320,781

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 and Chief Operating Officer, who serve as our principal executive and principal financial officer, respectively, has evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2016. Based upon such evaluation, our Chief Executive Officer and Chief Operating Officer have concluded that our disclosure controls and procedures were effective at the reasonable assurance level as of such date.

Internal Control Over Financial Reporting

Management's Report on Internal Control Over Financial Reporting

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

No change in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) occurred during the three months ended December 31, 2016 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 2017 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 2017 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 2017 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 2017 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 2017 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*

The exhibits filed as part of this Annual Report on Form 10-K are listed in the Exhibit Index immediately preceding such Exhibits, which Exhibit Index is incorporated herein by reference.

(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 20, 2017

By: /s/ Nancy Simonian, M.D.
Nancy Simonian, M.D.
President and Chief Executive Officer

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

Signature	Title	Date
/s/ Nancy Simonian, M.D. Nancy Simonian, M.D.	President, Chief Executive Officer and Director (*Principal Executive Officer*)	March 20, 2017
/s/ Kyle D. Kuvalanka Kyle D. Kuvalanka	Chief Operating Officer (*Principal Financial and Accounting Officer*)	March 20, 2017
/s/ Peter Wirth Peter Wirth	Chair of the Board of Directors	March 20, 2017
/s/ Stéphane Bancel Stéphane Bancel	Director	March 20, 2017
/s/ Marsha H. Fanucci Marsha H. Fanucci	Director	March 20, 2017
/s/ Amir Nashat, Ph.D. Amir Nashat, Ph.D.	Director	March 20, 2017
/s/ Robert T. Nelsen Robert T. Nelsen	Director	March 20, 2017
/s/ Sanj K. Patel Sanj K. Patel	Director	March 20, 2017
/s/ Vicki L Sato, Ph.D. Vicki L. Sato, Ph.D.	Director	March 20, 2017
/s/ Phillip A. Sharp, Ph.D. Phillip A. Sharp, Ph.D.	Director	March 20, 2017
/s/ Richard A. Young, Ph.D. Richard A. Young, Ph.D.	Director	March 20, 2017

EXHIBIT INDEX

Exhibit No.	Description	Incorporation by Reference			Filed with this 10-K
		Form	SEC Filing Date	Exhibit Number	
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	
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.				X
10.13*	Consulting Agreement dated August 8, 2012 by and between the Registrant and Richard A. Young, Ph.D., as amended				X
10.14*	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					
10.15+	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	
10.16+	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	
10.17+	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	
10.18+	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	
10.19+	Supply Management Agreement dated April 28, 2016 by and between the Registrant and TMRC Co., Ltd.	S-1^	6/3/16	10.18	
10.20	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	
Leases					
10.21	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

Exhibit No.	Description	Incorporation by Reference			Filed with this 10-K
		Form	SEC Filing Date	Exhibit Number	
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

\# 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.

Exhibit 10.12

September 8, 2016

Gerald Quirk
Via e-mail

Dear Gerald:

On behalf of Syros Pharmaceuticals, Inc. (the "Company"), I am pleased to extend the following offer and set forth the terms of your employment with the Company:

1. You will be employed to serve on a FULL-TIME basis as Chief Legal Officer effective September 26, 2016. As Chief Legal Officer you will report to Nancy Simonian, CEO and will be responsible for aligning and implementing the Company's overall legal strategy plus such other duties as may from time to time be assigned to you by the Company.

2. Your salary will be $365,000 per year, paid semi-monthly in arrears in accordance with the Company's normal payroll processes and subject to tax and other withholdings as required by law. Such salary may be adjusted from time to time in accordance with normal business practice and in the sole discretion of the Company.

3. You may participate in any and all bonus and benefit programs that the Company establishes and makes available to its employees from time to time, provided you are eligible under (and subject to all provisions of) the plan documents governing those programs. Specifically, you will be eligible to receive a 35% bonus in your first year of employment with the Company, prorated based on your start date and approved by the Board of Directors. Future bonus eligibility will be based on the Company's annual bonus plan and approved by the Board of Directors.

4. Without otherwise limiting the "at-will" nature of your employment, in the event your employment is terminated by the Company without Cause or by you for Good Reason (each as defined below), you shall be entitled to the base salary that has accrued and to which you are entitled as of the effective date of such termination, and further, subject to the conditions set forth in the second paragraph of this Section 4, the Company shall, for a period of nine (9) months following your termination date: (i) continue to pay you, in accordance with the Company's regularly established payroll procedure, your base salary as severance; and (ii) provided you are eligible for and timely elect to continue receiving group medical insurance pursuant to the "COBRA" law, continue to pay the share of the premium for health coverage that is paid by the Company for active and similarly-situated employees who receive the same type of coverage, unless the Company's provision of such COBRA payments will violate the nondiscrimination requirements of applicable law, in which case this benefit will not apply. If, within the three months prior to a Change in Control or in the twelve months following a Change in Control, the Company terminates your employment without Cause or you resign for Good Reason, the Company, subject to the conditions set forth in the second paragraph of this Section 4, will: (a) extend the severance benefits described in (i) and (ii) above for an additional three months, such that the total severance benefit period shall be one (1) year; (b) pay you a lump sum amount equal to your target bonus in effect for the fiscal year in which your separation from employment occurs; and (c) accelerate the vesting of all unvested stock options held by you as of the date your employment is terminated such that 100% of such options shall become fully vested and exercisable effective as of such date.

Notwithstanding the foregoing, you will not be entitled to receive any severance benefits unless, within sixty (60) days following the date of termination, you (i) have executed a severance and release of claims agreement in a form prescribed by the Company or persons affiliated with the Company (which will include, at a minimum, a release of all releasable claims and non-disparagement and cooperation obligations). Any severance payments shall be paid, or commence on the first payroll period following the date the release becomes effective (the "Payment Date"). Notwithstanding the foregoing, if the 60th day following the date of termination occurs in the calendar year following the calendar year of the termination, then the Payment Date shall be no earlier than January 1st of such subsequent calendar year.

For purposes of this Agreement, "Change in Control" means any transaction or series of related transactions (a) the result of which is a change in the ownership of the Company, such that more than 50% of the equity securities of the Company are acquired by any person or group (as such terms are defined for purposes of Section I3(d)(3) of the Securities Exchange Act of 1934, as amended) that does not own capital stock of the Company of the effective date of such change in control, (b) that results in the sale of all or substantially all of the assets of the Company, or (c) that results in the consolidation or merger of the Company with or into another corporation or corporations or other entity in which the Company is not the survivor (except any such corporation or entity controlled, directly or indirectly, by the Company).

"Cause" means: (a) your conviction of, or plea of guilty or nolo contendere to, any crime involving dishonesty or moral turpitude or any felony; or (b) you have (i) engaged in material dishonesty, willful misconduct or gross negligence, (ii) breached or threatened to breach either or both of the Ancillary Agreements (as defined below), (iii) materially violated a Company policy or procedure causing or threatening to cause substantial injury to the Company, and/or (iv) willfully refused to perform your assigned duties to the Company, following written notice of such refusal by the Company and a period of thirty (30) days to cure the same.

"Good Reason" means the occurrence of one or more of the following without your written consent: (a) a material reduction in your authority, duties and/or responsibilities as compared to your authority, duties and/or responsibilities in effect immediately prior to the occurrence of the event (for example, but not by way of limitation, this determination will include an analysis of whether you maintain at least the same level, scope and type of duties and responsibilities with respect to the management, strategy, operations and business of the Company), or (b) a material reduction in your base compensation as compared to your base compensation in effect immediately prior to the occurrence of the event; provided, however, that no such occurrence shall constitute Good Reason unless: (i) you give the Company a written notice of termination for Good Reason not more than ninety (90) days after the initial existence of the condition, (ii) the grounds for termination (if susceptible to correction) are not corrected by the Company within thirty (30) days of its receipt of such notice, and (iii) your termination of employment occurs within one (1) year following the Company's receipt of such notice.

5. You may be eligible for a maximum of three (3) weeks of vacation per calendar year to be taken at such times as may be approved by the Company. The number of vacation days for which you are eligible shall accrue at the rate of 1.25 days per month that you are employed during such calendar year.

6. Subject to the approval of the Board of Directors of the Company (the "Board"), the Company will grant to you an option (a "Time-Based Option") under the Company's 2016 Stock Incentive Plan (the "Plan") for the purchase of 105,000 shares of common stock of the Company ("Common Stock"), at a price per share equal to the closing price of the Common Stock on the date of Board approval, which option shall be granted within 30 days of your first day of employment. The Time-Based Option shall vest (i) as to 25% of the shares underlying the option on the one-year anniversary of your first day of employment, and (ii) as to the remaining shares underlying the option in equal monthly installments for the next 36 months thereafter, becoming fully vested on the fourth anniversary of your first day of employment, provided that you remain employed by us on the applicable vesting date. Subject to the approval of the Board, you shall also be granted

an option (a "Performance-Based Option") under the Plan to purchase an additional 35,000 shares of Common Stock of the Company, at a price per share equal to the closing price of the Common Stock on the date of Board approval, which option shall be granted within 30 days of your first day of employment and vest six years from your first day of employment, subject to accelerated vesting according to the following schedule: (i) 33% upon the earlier of (A) achievement of clinical proof of concept with a molecule beyond SY-1425 or (B) the start of the first pivotal trial; and (ii) 67% upon signing by the Company of a business development, collaboration or partnership agreement around the Company's platform or one of its product candidates, in each cased based on parameters approved by the Board, and provided that the Participant remains employed by the Company on the applicable vesting date.

7. Each of the Time-Based Option and the Performance-Based Option shall be subject to all terms and other provisions set forth in the Plan and in a separate option agreement.

8. You may be eligible to receive such future stock options grants as the Board shall deem appropriate.

9. You will be required to execute an Invention and Non-Disclosure Agreement and a Non-Competition and Non-Solicitation Agreement in the forms attached as Exhibit A and Exhibit B, respectively, as a condition of employment (such agreements are referred to as "Ancillary Agreements").

10. You represent that you are not bound by any employment contract, restrictive covenant or other restriction preventing you from entering into employment with or carrying out your responsibilities for the Company, or which is in any way inconsistent with the terms of this letter.

11. You agree to provide to the Company, within three days of your hire date, documentation of your eligibility to work in the Uinited States, as required by the Immigration Reform and Control Act of 1986. You may need to obtain a work visa in order to be eligible to work in the United States. If that is the case, your employment with the Company will be conditioned upon your obtaining a work visa in a timely manner as determined by the Company.

12. This letter shall not be construed as an agreement, either expressed or implied, to employ you for any stated term, and shall in no way alter the Company's policy of employment at will, under which both you and the Company remain free to terminate the employment relationship, with or without cause, at any time, with or without notice. Similarly, nothing in this letter shall be construed as an agreement, either express or implied, to pay you any compensation or grant you any benefit beyond the end of your employment with the Company.

This letter is intended to provide payments that are exempt from or compliant with 409A, and should be interpreted consistent with that intent.

THE REMAINDER OF THIS PAGE INTENTIONALLY LEFT BLANK

If you agree with the employment provisions of this letter, please sign the letter and exhibits, scan the signature pages and email to Leslie Kaufman at lkaufman@syros.com. If you do not accept this offer by September 12, 2016, this offer will be revoked.

Very truly yours,

/s/ Nancy Simonian
Name: Nancy Simonian Title: CEO

The foregoing correctly sets forth the terms of my employment by Syros Pharmaceuticals, Inc.

Date: September 9, 2016

/s/ Gerald Quirk
Gerald Quirk

Attachment A

Payments Subject to Section 409A

1. Subject to this Attachment A, any severance payments that may be due under the letter agreement shall begin only upon the date of your "separation from service" (determined as set forth below) which occurs on or after the termination of your employment. The following rules shall apply with respect to distribution of the severance payments, if any, to be provided to you under the letter agreement, as applicable:

(a) It is intended that each installment of the severance payments under the letter agreement provided under shall be treated as a separate "payment" for purposes of Section 409A of the Internal Revenue Code of 1986, as amended ("Section 409A"). Neither the Company nor you shall have the right to accelerate or defer the delivery of any such payments except to the extent specifically permitted or required by Section 409A.

(b) If, as of the date of your "separation from service" from the Company, you are not a "specified employee" (within the meaning of Section 409A), then each installment of the severance payments shall be made on the dates and terms set forth in the letter agreement.

(c) If, as of the date of your "separation from service" from the Company, you are a "specified employee" (within the meaning of Section 409A), then:

(i) Each installment of the severance payments due under the letter agreement that, in accordance with the dates and terms set forth herein, will in all circumstances, regardless of when your separation from service occurs, be paid within the short-term deferral period (as defined under Section 409A) shall be treated as a short-term deferral within the meaning of Treasury Regulation Section l.409A-l (b)(4) to the maximum extent permissible under Section 409A and shall be paid on the dates and terms set forth in the letter agreement; and

(ii) Each installment of the severance payments due under the letter agreement that is not described in this Attachment A, Section 1(c)(i) and that would, absent this subsection, be paid within the six-month period following your "separation from service" from the Company shall not be paid until the date that is six months and one day after such separation from service (or, if earlier, your death), with any such installments that are required to be delayed being accumulated during the six month period and paid in a lump sum on the date that is six months and one day following your separation from service and any subsequent installments, if any, being paid in accordance with the dates and terms set forth herein; provided, however, that the preceding provisions of this sentence shall not apply to any installment of payments if and to the maximum extent that that such installment is deemed to be paid under a separation pay plan that does not provide for a deferral

of compensation by reason of the application of Treasury Regulation 1.409A- 1(b)(9)(iii) (relating to separation pay upon an involuntary separation from service). Any installments that qualify for the exception under Treasury Regulation Section 1.409A-1(b)(9)(iii) must be paid no later than the last day of your second taxable year following the taxable year in which the separation from service occurs.

2. The determination of whether and when your separation from service from the Company has occurred shall be made and in a manner consistent with, and based on the presumptions set forth in, Treasury Regulation Section l.409A-l (h). Solely for purposes of this Attachment A, Section 2, “Company” shall include all persons with whom the Company would be considered a single employer under Section 414(b) and 414(c) of the Internal Revenue Code of 1986, as amended.

3. The Company makes no representation or warranty and shall have no liability to you or to any other person if any of the provisions of the letter agreement (including this Attachment) are determined to constitute deferred compensation subject to Section 409A but that do not satisfy an exemption from, or the conditions of, that section.

Exhibit A

INVENTION AND NON-DISCLOSURE AGREEMENT

This Agreement is made by and between Syros Pharmaceuticals, Inc., a Delaware corporation (hereinafter referred to collectively with its subsidiaries as the "Company"), and Gerald Quirk (the "Employee").

In consideration of the employment or the continued employment of the Employee by the Company, the Company and the Employee agree as follows:

1. Condition of Employment.

The Employee acknowledges that his/her employment and/or the continuance of that employment with the Company is contingent upon his/her agreement to sign and adhere to the provisions of this Agreement. The Employee further acknowledges that the nature of the Company's business is such that protection of its proprietary and confidential information is critical to the business' survival and success.

2. Proprietary and Confidential Information.

(a) The Employee agrees that all information and know-how, whether or not in writing, of a private, secret or confidential nature concerning the Company's business or financial affairs (collectively, "Proprietary Information") is and shall be the exclusive property of the Company. By way of illustration, but not limitation, Proprietary Information may include discoveries, inventions, products, product improvements, product enhancements, processes, methods, techniques, formulas, compositions, compounds, negotiation strategies and positions, projects, developments, plans (including business and marketing plans), research data, clinical data, financial data (including sales costs, profits, pricing methods), personnel data, computer programs (including software used pursuant to a license agreement), customer, prospect and supplier lists, and contacts at or knowledge of customers or prospective customers of the Company. The Employee will not disclose any Proprietary Information to any person or entity other than employees of the Company or use the same for any purposes (other than in the performance of his/her duties as an employee of the Company) without written approval by an officer of the Company, either during or after his/her employment with the Company, unless and until such Proprietary Information has become public knowledge without fault by the Employee. While employed by the Company, the Employee will use the Employee's best efforts to prevent unauthorized publication or disclosure of any of the Company's Proprietary Information.

(b) The Employee agrees that all files, documents, letters, memoranda, reports, records, data, sketches, drawings, models, laboratory notebooks, program listings, computer equipment or devices, computer programs or other written, photographic, or other tangible or intangible material containing Proprietary Information, whether created by the Employee or others, which shall come into his/her custody or possession, shall be and are the exclusive property of the Company to be used by the Employee only in the performance of his/her duties for the Company and shall not be copied or removed from the Company premises except in the pursuit of the business of the Company. All such materials or copies thereof and all tangible property of the Company in the custody or possession of the Employee shall be delivered to the Company, upon the earlier of (i) a request by the Company or (ii) termination of his/her employment. After such delivery, the Employee shall not retain any such materials or copies thereof or any such tangible property.

(c) The Employee agrees that his/her obligation not to disclose or to use information and materials of the types set forth in paragraphs 2(a) and 2(b) above, and his/her obligation to return materials and tangible property, set forth in paragraph 2(b) above, also extends to such types of information, materials and tangible property of customers of the Company or suppliers to the Company or other third parties who may have disclosed or entrusted the same to the Company or to the Employee in the course of the Company's business.

3. Developments.

(a) The Employee will make full and prompt disclosure to the Company of all discoveries, inventions, improvements, enhancements, processes, methods, techniques, developments, software, and works of authorship, whether patentable or not, which are created, made, conceived or reduced to practice by him/her or under his/her direction or jointly with others during his/her employment by the Company, whether or not during normal working hours or on the premises of the Company (all of which are collectively referred to in this Agreement as "Developments").

(b) The Employee agrees to assign and does hereby assign to the Company (or any person or entity designated by the Company) all his/her right, title and interest in and to all Developments and all related patents, patent applications, copyrights and copyright applications. However, this paragraph 3(b) shall not apply to Developments which do not relate to the business or research and development conducted or planned to be conducted by the Company at the time such Development is created, made, conceived or reduced to practice and which are made and conceived by the Employee not during normal working hours, not on the Company's premises and not using the Company's tools, devices, equipment or Proprietary Information. The Employee understands that, to the extent this Agreement shall be construed in accordance with the laws of any state which precludes a requirement in an employee agreement to assign certain classes of inventions made by an employee, this paragraph 3(b) shall be interpreted not to apply to any invention which a court rules and/or the Company agrees falls within such classes. The Employee also hereby waives all claims to moral rights in any Developments.

(c) The Employee agrees to cooperate fully with the Company, both during and after his/her employment with the Company, with respect to the procurement, maintenance and enforcement of copyrights, patents and other intellectual property rights (both in the United States and foreign countries) relating to Developments. The Employee shall sign all papers, including, without limitation, copyright applications, patent applications, declarations, oaths, formal assignments, assignments of priority rights, and powers of attorney, which the Company may deem necessary or desirable in order to protect its rights and interests in any Development. The Employee further agrees that if the Company is unable, after reasonable effort, to secure the signature of the Employee on any such papers, any executive officer of the Company shall be entitled to execute any such papers as the agent and the attorney-in-fact of the Employee, and the Employee hereby irrevocably designates and appoints each executive officer of the Company as his/her agent and attorney-in-fact to execute any such papers on his/her behalf, and to take any and all actions as the Company may deem necessary or desirable in order to protect its rights and interests in any Development, under the conditions described in this sentence.

4. Other Agreements.

The Employee represents that, except as the Employee has disclosed in writing to the Company, the Employee is not bound by the terms of any agreement with any previous employer or other party to refrain from using or disclosing any trade secret or confidential or proprietary information in the course of his/her employment with the Company, to refrain from competing, directly or indirectly, with the business of such previous employer or any other party or to refrain from soliciting employees, customers or suppliers of such previous employer or other party. The Employee further represents that his/her performance of all the terms of this Agreement and the performance of his/her duties as an employee of the Company do not and will not conflict with or breach any agreement with any prior employer or other party to which the Employee is a party (including without limitation any nondisclosure or non-competition agreement), and that the Employee will not disclose to the Company or induce the Company to use any confidential or proprietary information or material belonging to any previous employer or others.

5. United States Government Obligations.

The Employee acknowledges that the Company from time to time may have agreements with other persons or with the United States Government, or agencies thereof, which impose obligations or restrictions on the Company regarding inventions made during the course of work under such agreements or regarding the confidential nature of such work. The Employee agrees to be bound by all such obligations and restrictions which are made known to the Employee and to take all action necessary to discharge the obligations of the Company under such agreements.

6. Miscellaneous.

(a) Equitable Remedies. The restrictions contained in this Agreement are necessary for the protection of the business and goodwill of the Company and are considered by the Employee to be reasonable for such purpose. The Employee agrees that any breach of this Agreement is likely to cause the Company substantial and irrevocable damage which is difficult to measure. Therefore, in the event of any such breach or threatened breach, the Employee agrees that the Company, in addition to such other remedies which may be available, shall have the right to obtain an injunction from a court restraining such a breach or threatened breach and the right to specific performance of the provisions of this Agreement and the Employee hereby waives the adequacy of a remedy at law as a defense to such relief.

(b) Obligations to Third Parties. The Employee acknowledges and represents that this agreement and the Employee's employment with the Company will not violate any continuing obligation the Employee has to any former employer or other third party.

(c) Disclosure of this Agreement. The Employee hereby authorizes the Company to notify others, including but not limited to customers of the Company and any of the Employee's future employers or prospective business associates, of the terms and existence of this Agreement and the Employee's continuing obligations to the Company hereunder.

(d) Not Employment Contract. The Employee acknowledges that this Agreement does not constitute a contract of employment, does not imply that the Company will continue his/her employment for any period of time and does not change the at-will nature of his/her employment.

(e) Successors and Assigns. This Agreement shall be binding upon and inure to the benefit of both parties and their respective successors and assigns, including any corporation with which, or into which, the Company may be merged or which may succeed to the Company's assets or business, provided, however, that the obligations of the Employee are personal and shall not be assigned by him or her. The Employee expressly consents to be bound by the provisions of this Agreement for the benefit of the Company or any subsidiary or affiliate thereof to whose employ the Employee may be transferred without the necessity that this Agreement be re-signed at the time of such transfer.

(f) Severability. In case any provision of this Agreement shall be invalid, illegal or otherwise unenforceable, the validity, legality and enforceability of the remaining provisions shall in no way be affected or impaired thereby.

(g) Waivers. No delay or omission by the Company in exercising any right under this Agreement will operate as a waiver of that or any other right. A waiver or consent given by the Company on any one occasion is effective only in that instance and will not be construed as a bar to or waiver of any right on any other occasion.

(h) Governing Law. This Agreement shall be governed by and construed in accordance with the laws of the Commonwealth of Massachusetts (without reference to the conflicts of laws provisions thereof). Any action, suit, or other legal proceeding which is commenced to resolve any matter arising under or relating to any provision of this Agreement shall be commenced only in a court of the Commonwealth of Massachusetts (or, if appropriate, a federal court located within Massachusetts), and the Company and the Employee each consents to the jurisdiction of such a court. The Company and the Employee each hereby irrevocably waive any right to a trial by jury in any action, suit or other legal proceeding arising under or relating to any provision of this Agreement.

(i) Entire Agreement; Amendment. This Agreement supersedes all prior agreements, written or oral, between the Employee and the Company relating to the subject matter of this Agreement. This Agreement may not be modified, changed or discharged in whole or in part, except by an agreement in writing signed by the Employee and the Company. The Employee agrees that any change or changes in his/her duties, salary or compensation after the signing of this Agreement shall not affect the validity or scope of this Agreement.

(j) Captions. The captions of the sections of this Agreement are for convenience of reference only and in no way define, limit or affect the scope or substance of any section of this Agreement.

THE EMPLOYEE ACKNOWLEDGES THAT HE/SHE HAS CAREFULLY READ THIS AGREEMENT AND UNDERSTANDS AND AGREES TO ALL OF THE PROVISIONS IN THIS AGREEMENT.

WITNESS our hands and seals:

SYROS PHARMACEUTICALS, INC.

Date: _____ By: _____

Name: Nancy Simonian

Title: CEO

Date: _____ _____

Gerald Quirk

Exhibit B

NON-COMPETITION AND NON-SOLICITATION AGREEMENT

This Agreement is made between Syros Pharmaceuticals, Inc., a Delaware corporation (hereinafter referred to collectively with its subsidiaries as the "Company"), and Gerald Quirk.

For good consideration and in consideration of the employment or continued employment of the Employee by the Company, including the equity consideration in the Company, the Employee and the Company agree as follows:

1. Non-Competition and Non-Solicitation. While the Employee is employed by the Company and for a period of one year after the termination or cessation of such employment for any reason, the Employee will not directly or indirectly:

(a) Engage or assist others in engaging in any business or enterprise (whether as owner, partner, officer, director, employee, consultant, investor, lender or otherwise, except as the holder of not more than 1% of the outstanding stock of a publicly-held company) that is competitive with the Company's business, including but not limited to any business or enterprise that develops, manufactures, markets, licenses, sells or provides any product or service that competes with any product or service developed, manufactured, marketed, licensed, sold or provided, or planned to be developed, manufactured, marketed, licensed, sold or provided, by the Company while the Employee was employed by the Company; or

Notwithstanding the foregoing, Section l(a) shall not preclude the Employee from becoming an employee of, or from otherwise providing services to, a separate division or operating unit of a multi-divisional business or enterprise (a "Division") if: (i) the Division by which the Employee is employed, or to which the Employee provides services, is not competitive with the Company's business (within the meaning of Section l (a)), (ii) the Employee does not provide services, directly or indirectly, to any other

division or operating unit of such multi divisional business or enterprise which is competitive with the Company's business (within the meaning of Section l(a)) (individually, a “Competitive Division” and collectively, the “Competitive Divisions”) and (iii) the Competitive Divisions, in the aggregate, accounted for less than one-third of the multi-divisional business or enterprises' consolidated revenues for the fiscal year, and each subsequent quarterly period, prior to the Employee's commencement of employment with the Division.

(b) Either alone or in association with others, solicit, divert or take away, or attempt to divert or take away, the business or patronage of any of the clients, customers, or business partners of the Company which were contacted, solicited, or served by the Company during the 12-month period prior to the termination or cessation of the Employee's employment with the Company; or

(c) Either alone or in association with others: (i) solicit, induce or attempt to induce, any employee or independent contractor of the Company to terminate his or her employment or other engagement with the Company, or (ii) solicit for employment or

engagement as an independent contractor any person who was employed or otherwise engaged by the Company at any time during the term of the Employee's employment with the Company; provided, that this clause (ii) shall not apply to the solicitation of any individual whose employment or other engagement with the Company has been terminated for a period of six months or longer.

(d) Extension. If the Employee violates the provisions of any of the preceding paragraphs of this Section 1, the Employee shall continue to be bound by the restrictions set forth in such paragraph until a period of one year has expired without any violation of such provisions.

2. Miscellaneous.

(a) Equitable Remedies. The restrictions contained in this Agreement are necessary for the protection of the business and goodwill of the Company and are considered by the Employee to be reasonable for such purpose. The Employee agrees that any breach of this Agreement is likely to cause the Company substantial and irrevocable damage which is difficult to measure. Therefore, in the event of any such breach or threatened breach, the Employee agrees that the Company, in addition to such other remedies which may be available, shall have the right to obtain an injunction from a court restraining such a breach or threatened breach and the right to specific performance of the provisions of this Agreement and the Employee hereby waives the adequacy of a remedy at law as a defense to such relief.

(b) Obligations to Third Parties. The Employee acknowledges and represents that this agreement and the Employee's employment with the Company will not violate any continuing obligation the Employee has to any former employer or other third party.

(c) Disclosure of this Agreement. The Employee hereby authorizes the Company to notify others, including but not limited to customers of the Company and any of the Employee's future employers or prospective business associates, of the terms and existence of this Agreement and the Employee's continuing obligations to the Company hereunder.

(d) Not Employment Contract. The Employee acknowledges that this Agreement does not constitute a contract of employment, does not imply that the Company will continue his/her employment for any period of time and does not change the at-will nature of his/her employment.

(e) Successors and Assigns. This Agreement shall be binding upon and inure to the benefit of both parties and their respective successors and assigns, including any corporation with which, or into which, the Company may be merged or which may succeed to the Company's assets or business, provided, however, that the obligations of the Employee are personal and shall not be assigned by him or her. The Employee expressly consents to be bound by the provisions of this Agreement for the benefit of the Company or any subsidiary or affiliate thereof to whose employ the Employee may be transferred without the necessity that this Agreement be re-signed at the time of such transfer. Notwithstanding the foregoing, if the Company is merged with or into a third party which is engaged in multiple lines of business, or if a third party engaged in multiple lines of business succeeds to the Company's assets or business, then for purposes of Section 1(a), the term “Company” shall mean and refer to the business of

the Company as it existed immediately prior to such event and as it subsequently develops and not to the third party's other businesses.

(f) Interpretation. If any restriction set forth in Section 1 is found by any court of competent jurisdiction to be unenforceable because it extends for too long a period of time or over too great a range of activities or in too broad a geographic area, it shall be interpreted to extend only over the maximum period of time, range of activities or geographic area as to which it may be enforceable.

(g) Severability. In case any provision of this Agreement shall be invalid, illegal or otherwise unenforceable, the validity, legality and enforceability of the remaining provisions shall in no way be affected or impaired thereby.

(h) Waivers. No delay or omission by the Company in exercising any right under this Agreement will operate as a waiver of that or any other right. A waiver or consent given by the Company on any one occasion is effective only in that instance and will not be construed as a bar to or waiver of any right on any other occasion.

(i) Governing Law. This Agreement shall be governed by and construed in accordance with the laws of the Commonwealth of Massachusetts (without reference to the conflicts of laws provisions thereof). Any action, suit, or other legal proceeding which is commenced to resolve any matter arising under or relating to any provision of this Agreement shall be commenced only in a court of the Commonwealth of Massachusetts (or, if appropriate, a federal court located within Massachusetts), and the Company and the Employee each consents to the jurisdiction of such a court. The Company and the Employee each hereby irrevocably waive any right to a trial by jury in any action, suit or other legal proceeding arising under or relating to any provision of this Agreement.

G) Entire Agreement; Amendment. This Agreement supersedes all prior agreements, written or oral, between the Employee and the Company relating to the subject matter of this Agreement. This Agreement may not be modified, changed or discharged in whole or in part, except by an agreement in writing signed by the Employee and the Company. The Employee agrees that any change or changes in his/her duties, salary or compensation after the signing of this Agreement shall not affect the validity or scope of this Agreement.

(k) Captions. The captions of the sections of this Agreement are for convenience of reference only and in no way define, limit or affect the scope or substance of any section of this Agreement.

[Remainder of this page intentionally left blank.]

THE EMPLOYEE ACKNOWLEDGES THAT HE/SHE HAS CAREFULLY READ THIS AGREEMENT AND UNDERSTANDS AND AGREES TO ALL OF THE PROVISIONS IN THIS AGREEMENT.

WITNESS our hands and seals:

SYROS PHARMACEUTICALS, INC.

Date: _____ By: _____

Name: Nancy Simonian
Title: CEO

Date: _____ _____

Gerald Quirk

Exhibit 10.13

CONSULTING AGREEMENT

THIS CONSULTING AGREEMENT (the "Agreement"), made this 8th day of August, 2012 is entered into by LS22, Inc., a Delaware corporation with its principal place of business at One Memorial Drive, 7th Floor, Cambridge, MA 02142 (the "Company"), and Richard A. Young, PhD., (the "Consultant"). The Consultant is a Member of the Whitehead Institute for Biomedical Research ("WIBR") and faculty member in the Department of Biology of the Massachusetts Institute of Technology ("MIT").

INTRODUCTION

The Company desires to retain the services of the Consultant and the Consultant desires to perform certain services for the Company. In consideration of the mutual covenants and promises contained herein and other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged by the parties hereto, the parties agree as follows:

1. Services. The Consultant agrees to perform such consulting, advisory and related services to and for the Company as may be reasonably requested from time to time by the Company. The Consultant agrees to devote up to one (1) day per week to the performance of such services. Without limiting the additional terms and conditions of Section 7 below, during the Consultation Period (as defined below), the Consultant shall not knowingly engage in any activity that has a conflict of interest with the Company, including any competitive employment, business, or other activity, and he shall not knowingly assist any other person or organization that competes, or intends to compete, with the Company, it being further acknowledged and understood by the Company that Consultant is currently involved in those endeavors listed on Annex 1 hereto.

The Whitehead Institute Uniform Consulting Agreement Provisions ("Standard Provisions") are attached hereto as Exhibit A and are incorporated herein by reference. The parties agree that the Standard Provisions are an integral part of this Agreement and this Agreement shall have no force or effect unless the Standard Provisions are signed by both parties. The parties hereto agree to abide by such Standard Provisions and further agree that in the event of any conflict between this Agreement and the Standard Provisions, the Standard Provisions shall govern and prevail.

2 . Term. This Agreement shall commence on the date hereof and shall continue until August 8, 2016 (such period, as it may be extended, being referred to as the "Consultation Period"), unless sooner terminated in accordance with the provisions of Section 4.

3. Compensation.

3.1 Equity Compensation. Subject to approval by the Board of Directors of the Company, in consideration for the performance of the services hereunder, the Consultant shall be awarded a grant of 1,600,000 shares of restricted common stock, $0.001 par value per share, of the Company ("Common Stock"), having a purchase price equal to the fair market value of the Common Stock on the date of grant ($0.001 per share) and having such other terms and conditions, including with respect to forfeiture and other transfer restrictions in favor of the Company, as shall be set forth in a Restricted Stock Agreement by and between the Consultant and the Company.

3.2 Fees. The Company will not pay the Consultant any consulting fees before the Qualified Financing Date (as defined below). After the Qualified Financing Date and before the Second Qualified Financing Date (as defined below), the Company shall pay to the Consultant consulting fees of $25,000 per year, payable in equal quarterly installments. From and after the Second Qualified Financing Date, the Company shall pay to the Consultant consulting fees of $50,000 per year, payable in equal quarterly installments. Payment for any partial quarter shall be prorated.

For purposes of this Agreement, "Qualified Financing Date" shall mean the first date on which the Company receives aggregate gross proceeds equal to or exceeding $750,000 from the sale to one or more third parties of shares of its capital stock, or notes or other indebtedness that is convertible into or exercisable for shares of its capital stock, in a venture capital transaction. For purposes of this Agreement, "Second Qualified Financing Date" shall mean the first date on which the Company receives aggregate gross proceeds equal to or exceeding $12,500,000 from the sale to one or more third parties of its capital stock, or notes or other indebtedness that is convertible into or exercisable for shares of its capital stock, in a venture capital transaction.

3.3 Reimbursement of Expenses. The Company shall reimburse the Consultant for all reasonable and necessary expenses incurred or paid by the Consultant in connection with, or related to, the performance of his services under this Agreement. The Consultant shall submit to the Company itemized monthly statements, in a form satisfactory to the Company, of such expenses incurred in the previous month. The Company shall pay to the Consultant amounts shown on each such statement within 30 days after receipt thereof.

3.4 Benefits. The Consultant shall not be entitled to any benefits, coverages or privileges, including, without limitation, social security, unemployment, medical or pension payments, made available to employees of the Company.

4. Termination. The Company may, without prejudice to any right or remedy it may have due to any failure of the Consultant to perform his obligations under this Agreement, terminate the Consultation Period upon 30 days' prior written notice to the Consultant. The Consultant may, without prejudice to any right or remedy it may have due to any failure of the Company to perform its obligations under this Agreement, terminate the Consultation Period upon 90 days' prior written notice to the Company. In the event of such termination, the Consultant shall be entitled to payment for services performed and expenses paid or incurred prior to the effective date of termination, subject to the limitation on reimbursement of expenses set forth in Section 3.2. Such payments shall constitute full settlement of any and all claims of the Consultant of every description against the Company. Notwithstanding the foregoing, the Company may terminate the Consultation Period, effective immediately upon receipt of written notice, if the Consultant breaches or threatens to breach any provision of Section 6 or Section 7, and the Consultant may terminate the Consultation Period, effective immediately upon receipt of written notice, if the Company breaches any provision of Section 3. The provisions of Sections 4, 6, 7, 8, 10 and 14 shall survive any termination of this Agreement.

5. Cooperation. The Consultant shall use his best efforts in the performance of his obligations under this Agreement. The Company shall provide such access to its information and

property as may be reasonably required in order to permit the Consultant to perform his obligations hereunder. The Consultant shall cooperate with the Company's personnel, shall not interfere with the conduct of the Company's business and shall observe all rules, regulations and security requirements of the Company concerning the safety of persons and property.

6. Inventions and Proprietary Information.

6.1 Inventions.

(a) All inventions, discoveries, computer programs, data, technology, designs, innovations and improvements (whether or not patentable and whether or not copyrightable) ("Inventions") which are made, conceived, reduced to practice, created, written, designed or developed by the Consultant, solely or jointly with others and whether during normal business hours or otherwise, (i) during the Consultation Period that result from the performance of Consultant's services and if related to the business of the Company or (ii) after the Consultation Period if resulting or directly derived from Proprietary Information (as defined below), shall be the sole property of the Company. The Consultant hereby assigns to the Company all Inventions and any and all related patents, copyrights, trademarks, trade names, and other industrial and intellectual property rights and applications therefor, in the United States and elsewhere and appoints any officer of the Company as his duly authorized attorney to execute, file, prosecute and protect the same before any government agency, court or authority. Upon the request of the Company and at the Company's expense, the Consultant shall execute such further assignments, documents and other instruments as may be necessary or desirable to fully and completely assign all Inventions to the Company and to assist the Company in applying for, obtaining and enforcing patents or copyrights or other rights in the United States and in any foreign country with respect to any Invention. The Consultant also hereby waives all claims to moral rights in any Inventions.

(b) The Consultant shall promptly disclose to the Company all Inventions and will maintain adequate and current written records (in the form of notes, sketches, drawings and as may be specified by the Company) to document the conception and/or first actual reduction to practice of any Invention. Such written records shall be available to and remain the sole property of the Company at all times.

6.2 Proprietary Information.

(a) The Consultant acknowledges that his relationship with the Company is one of high trust and confidence and that in the course of his service to the Company he will have access to and contact with Proprietary Information. The Consultant agrees that he will not, during the Consultation Period or at any time thereafter, disclose to others, or use for his benefit or the benefit of others, any Proprietary Information or Invention.

(b) For purposes of this Agreement, Proprietary Information shall mean, by way of illustration and not limitation, all information (whether or not patentable and whether or not copyrightable) owned, possessed or used by the Company, including, without limitation, any Invention, formula, vendor information, customer information, apparatus, equipment, trade secret, process, research, report, technical data, know-how, computer program, software, software documentation, hardware design, technology, marketing or business plan, forecast, unpublished

financial statement, budget, license, price, cost and employee list that is communicated to, learned of, developed or otherwise acquired by the Consultant in the course of his service as a consultant to the Company.

(c) The Consultant's obligations under this Section 6.2 shall not apply to any information (none of which shall be deemed Proprietary Information) that (i) was known to Consultant prior to it being furnished to the Consultant by or on behalf of the Company provided that such information was or is not known to Consultant to be subject to another confidentiality agreement with, or other contractual, legal or fiduciary obligation of confidentiality to the Company, (ii) is developed by Consultant independently of the Proprietary Information disclosed to Consultant by the Company as demonstrated by the Consultant through third party written records, (iii) is acquired by Consultant on a non-confidential basis from any person entitled to make disclosure to Consultant unless such person is under an obligation of confidentiality to Company which is known to Consultant, (iv) is or becomes known to the general public under circumstances involving no breach by the Consultant or others of the terms of this Section 6.2, (v) is generally disclosed to third parties by the Company without restriction on such third parties, (vi) is approved for release by written authorization of the Board of Directors of the Company, or (vii) Consultant is obligated to produce pursuant to an order of a court of competent jurisdiction or a valid administrative or Congressional subpoena, provided that the Consultant promptly notify Company and cooperate reasonably with Company's efforts to contest or limit the scope of such order.

(d) Upon termination of this Agreement or at any other time upon request by the Company, the Consultant shall promptly deliver to the Company all records, files, memoranda, notes, designs, data, reports, price lists, customer lists, drawings, plans, computer programs, software, software documentation, sketches, laboratory and research notebooks and other documents (and all copies or reproductions of such materials) relating to the business of the Company.

(e) The Consultant represents that his retention as a consultant with the Company and his performance under this Agreement does not, and shall not, breach any agreement that obligates him to keep in confidence any trade secrets or confidential or proprietary information of his or of any other party or to refrain from competing, directly or indirectly, with the business of any other party. The Consultant shall not disclose to the Company any trade secrets or confidential or proprietary information of any other party.

(f) The Consultant acknowledges that the Company from time to time may have agreements with other persons or with the United States Government, or agencies thereof, that impose obligations or restrictions on the Company regarding inventions made during the course of work under such agreements or regarding the confidential nature of such work. The Consultant agrees to be bound by all such obligations and restrictions that are known to him and to take all action necessary to discharge the obligations of the Company under such agreements.

7. Non-Competition and Non-Solicitation.

7.1 Restrictions. During the term of this Agreement and for a period of one (1) year after termination of the Agreement, the Consultant will not directly or indirectly:

(a) Engage or assist others in engaging in any business or enterprise (whether as owner, partner, officer, director, employee, consultant, investor, lender or otherwise, except as the holder of not more than 1% of the outstanding stock of a publicly-held company) that is competitive with the Company's business, including but not limited to any business or enterprise that develops, manufactures, markets, licenses, sells or provides any product or service that competes with any product or service developed, manufactured, marketed, licensed, sold or provided, or planned to be developed, manufactured, marketed, licensed, sold or provided, by the Company while the Consultant was employed by the Company; or

(b) Either alone or in association with others, divert or take away, or attempt to divert or take away, the business or patronage of any of the clients, customers, or business partners of the Company which were contacted, solicited, or served by the Company during the 12-month period prior to the termination or cessation of the Consultant's services with the Company; or

(c) Either alone or in association with others (i) solicit, induce or attempt to induce, any employee or independent contractor of the Company to terminate his or her employment or other engagement with the Company, or (ii) hire, or recruit or attempt to hire, or engage or attempt to engage as an independent contractor, any person who was employed or otherwise engaged by the Company at any time during the term of the Consultant's services with the Company; provided, that this clause (ii) shall not apply to the recruitment or hiring or other engagement of any individual whose employment or other engagement with the Company has been terminated for a period of six months or longer.

7.2 Extension. If the Consultant violates the provisions of Section 7.1, the Consultant shall continue to be bound by the restrictions set forth in such paragraph until a period of one (1) year has expired without any violation of such provisions.

7.3 Company's Business. For purposes of this Agreement, the "Company's business" shall mean the discovery and development of therapeutic, diagnostic, and/or research products related to mechanisms by which gene transcription is regulated, provided, however, that the "Company's business" shall exclude the discovery and development of therapeutic, diagnostic, and/or research products that target BET bromodomains and histone deacetylases 1, 2 and 6.

8. Remedies. The Consultant acknowledges that any breach of the provisions of Section 6 or 7 could result in serious and irreparable injury to the Company for which the Company cannot be adequately compensated by monetary damages alone. The Consultant agrees, therefore, that in the event of such breach, in addition to any other remedy it may have, the Company shall be entitled to enforce the specific performance of this Agreement by the Consultant and to seek both temporary and permanent injunctive relief (to the extent permitted by law) without the necessity of proving actual damages.

9. Independent Contractor Status. The Consultant shall perform all services under this Agreement as an "independent contractor" and not as an employee or agent of the Company. The Consultant is not authorized to assume or create any obligation or responsibility, express or implied, on behalf of, or in the name of, the Company or to bind the Company in any manner.

10. Notices. All notices required or permitted under this Agreement shall be in writing and shall be deemed effective upon personal delivery or upon deposit in the United States Post Office, by registered or certified mail, postage prepaid, addressed to the other party at the address shown above, or at such other address or addresses as either party shall designate to the other in accordance with this Section 10.

11. Pronouns. Whenever the context may require, any pronouns used in this Agreement shall include the corresponding masculine, feminine or neuter forms, and the singular forms of nouns and pronouns shall include the plural, and vice versa.

12. Entire Agreement. This Agreement constitutes the entire agreement between the parties and supersedes all prior agreements and understandings, whether written or oral, relating to the subject matter of this Agreement.

13. Amendment. This Agreement may be amended or modified only by a written instrument executed by both the Company and the Consultant.

14. Governing Law. This Agreement shall be construed, interpreted and enforced in accordance with the laws of the Commonwealth of Massachusetts.

15. Successors and Assigns. This Agreement shall be binding upon, and inure to the benefit of, both parties and their respective successors and assigns, including any corporation with which, or into which, the Company may be merged or which may succeed to its assets or business, provided, however, that the obligations of the Consultant are personal and shall not be assigned by him.

16. Miscellaneous.

16.1 No delay or omission by the Company in exercising any right under this Agreement shall operate as a waiver of that or any other right. A waiver or consent given by the Company on any one occasion shall be effective only in that instance and shall not be construed as a bar or waiver of any right on any other occasion.

16.2 The captions of the sections of this Agreement are for convenience of reference only and in no way define, limit or affect the scope or substance of any section of this Agreement. In the event that any provision of this Agreement shall be invalid, illegal or otherwise unenforceable, the validity, legality and enforceability of the remaining provisions shall in no way be affected or impaired thereby.

[*Remainder of page intentionally left blank*]

IN WITNESS WHEREOF, the parties hereto have executed this Agreement as of the day and year set forth above.

LS22, Inc.

By: /s/ Douglas Cole, M.D.
Name: Douglas Cole, M.D.
Title: President

CONSULTANT

/s/ Richard A. Young, Ph.D.
Richard A. Young, Ph.D.

WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH UNIFORM CONSULTING AGREEMENT PROVISIONS

1. The Whitehead Institute for Biomedical Research ("WHITEHEAD") is a non-profit biomedical research institute having a business address of Nine Cambridge Center, Cambridge, Massachusetts 02142. These Uniform Consulting Agreement Provisions (the "Uniform Provisions") are attached to an agreement (the "Agreement") under which a Member of WHITEHEAD (the "Consultant") has agreed to provide consulting services to the company named in the Agreement (the "Company"). The Consultant and the Company agree that the Agreement shall have no force or effect unless these Uniform Provisions are signed by both parties and attached to the Agreement. By signing the Uniform Provisions, the Consultant and the Company agree to abide by them, and also agree that if anything in the Agreement is inconsistent with the Uniform Provisions, the Uniform Provisions shall govern.

2. The Agreement shall disclose all compensation of whatever kind that is to be provided to the Consultant in connection with the consulting services. The Agreement shall disclose the time commitment for the consulting services, which may not exceed one day per week for all outside activities of the Member of WHITEHEAD.

3. The Consultant's services for the Company shall consist only of the exchange of ideas and provision of advice; the Consultant shall not direct or conduct research for or on behalf of the Company.

4. The Company acknowledges that the Consultant is a Member of WHITEHEAD and is subject to WHITEHEAD's policies, including policies concerning consulting, conflicts of interest, and intellectual property. In accordance with WHITEHEAD policy, the Consultant may disclose to the Company any information that the Consultant would normally freely disclose to other members of the scientific community at large, whether by publication, by presentation at seminars, or in informal scientific discussions. However, the Consultant shall not disclose to the Company information that (i) is proprietary to WHITEHEAD and (ii) is not generally available to the public, except through formal technology transfer procedures.

5. Subject to the terms of paragraph 6, below, the Consultant may assign to the Company any right, title and interest the Consultant may have in any invention, discovery, improvement, or other intellectual property which the Consultant (whether alone or with others) develops (i) during the course of performing consulting services for the Company under the Agreement and (ii) outside the course of the Consultant's activities as a Member of WHITEHEAD.

6. The Company shall have no rights by reason of the Agreement in any publication, invention, discovery, improvement, or other intellectual property whatsoever, whether or not publishable, patentable, or copyrightable, which is developed as a result of a program of research financed, in whole or in part, by funds provided by or under the control of WHITEHEAD. The Company also acknowledges and agrees that it will enjoy no priority or advantage as a result of the consultancy created by the Agreement in gaining access, whether by license or otherwise, to any proprietary information or intellectual property that arises from any research undertaken by the Consultant in his or her capacity as a Member of WHITEHEAD.

7. The Company agrees, at its sole expense, to defend WHITEHEAD against, and to indemnify and hold WHITEHEAD harmless from, any claim, liability, judgment, cost, expense, damage, deficiency, loss, or obligation, of any kind or nature (including without limitation reasonable attorneys' fees and other costs and expenses of defense) relating to a claim or suit by a third party against WHITEHEAD, either arising from the Agreement, the Consultant's performance of services for the Company under the Agreement, or any Company products or services which result from the Consultant's performance of services under the Agreement.

8. Nothing in the Agreement shall affect the Consultant's right to use, disseminate, or publish any information that (i) is or becomes available to the public through no breach of the Agreement by the Consultant; (ii) is obtained by the Consultant from a third party who had the legal right to disclose the information to the Consultant; (iii) is already in the possession of the Consultant on the date the Agreement becomes effective; or (iv) is required to be disclosed by law, government regulation, or court order, provided that the Consultant takes reasonable steps to provide the Company with sufficient prior notice to allow the Company to consent to the disclosure or seek a protective order. In addition, the Company's confidential information does not include information generated by the Consultant (whether alone or with others) unless the Consultant generated the information (i) during the course of performing consulting services for the Company under the Agreement and (ii) outside the course of the Consultant's activities as a Member of WHITEHEAD.

9. The Company acknowledges and agrees that nothing in the Agreement shall affect the Consultant's obligations to WHITEHEAD, the Consultant's research on behalf of WHITEHEAD, or research collaborations in which the Consultant is a participant, and that the Agreement shall have no effect upon transfers (by way of license or otherwise) to third parties of materials or intellectual property developed in whole or in part by the Consultant as a Member of WHITEHEAD.

10. Paragraphs 7, 8, 9, 10, 12, 13, and 14 of these Uniform Provisions shall survive termination of the Agreement.

11. The Company may use the Consultant's name, and in doing so may cite the Consultant's relationship with WHITEHEAD, so long as any such usage (i) is limited to reporting factual events or occurrences only, and (ii) is made in a manner that could not reasonably constitute an endorsement of the Company or of any Company program, product or service. However, the Company shall not use the Consultant's name or WHITEHEAD's name in any press release, or quote the Consultant in any company materials, or otherwise use the Consultant's name or WHITEHEAD's name in a manner not specifically permitted by the preceding sentence, unless in each case the Company obtains in advance WHITEHEAD's written consent, and, in the case of the use of the Consultant's name, the Consultant's consent as well.

12. The Consultant and the Company acknowledge that (i) the Consultant is entering into the Agreement and these Uniform Provisions in the Consultant's individual capacity and not as a Member of WHITEHEAD, (ii) WHITEHEAD is not a party to the Agreement or the Uniform Provisions and has no liability or obligation under them, and (iii) WHITEHEAD is an intended third-party beneficiary of the Agreement and the Uniform Provisions are for WHITEHEAD's benefit and are enforceable by WHITEHEAD in its own name.

13. These Uniform Provisions shall be in effect for the full term of the Agreement. The Company and the Consultant agree that any amendment of the Agreement (including, without limitation, any extension of the Agreement's term or any change in the consideration to be provided to the Consultant under the Agreement) or any other departure from the terms or conditions of the Agreement must be signed by the Consultant and an authorized representative of the Company, and also is subject to WHITEHEAD's prior written approval.

14. If any of these Uniform Provisions is adjudicated to be invalid, unenforceable, contrary to, or prohibited under applicable laws or regulations of any jurisdiction, the Agreement shall terminate as of the date such adjudication is effective.

COMPANY

By: /s/ Douglas Cole
Name: Douglas Cole
Title: President

CONSULTANT

By: /s/ Richard A. Young
Name: Richard A. Young, Ph.D.

ANNEX 1

Existing Endeavors

1. Presently engaged under consulting arrangements with:

   · Enzon Pharmaceuticals, Inc.

CONSULTING AGREEMENT-FIRST AMENDMENT

This First Amendment to the CONSULTING AGREEMENT (the "First Amendment"), made this 3rd day of December, 2012 is entered into by Syros Pharmaceuticals, Inc. (f/k/a LS22, Inc.), a Delaware corporation with its principal place of business at One Memorial Drive, 7th. Floor, Cambridge, MA 02142 (the "Company"), and Richard A. Young, Ph.D. (the "Consultant").

WHEREAS, Company and Consultant entered into a Consulting Agreement dated August 8, 2012 (the "Agreement"); and

WHEREAS, Company and Consultant desire to amend the Term of the Agreement under Section 2 and the Compensation under Section 3.

NOW THEREFORE, in consideration of the mutual covenants, conditions and agreements set forth herein, and for such other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties hereto agree as follows:

I. Defined Terms. Unless otherwise defined herein, the meaning of the terms used herein shall have the same meanings set forth in the Agreement.

2A. Term. Section 2 of the Agreement is deleted and replaced in its entirety with the following:

"2. Term. This Agreement shall commence July 3, 2012 and shall continue until July 3, 2016 (such period, as it may be extended, being referred to as the "Consultation Period"), unless sooner terminated in accordance with the provisions of Section 4."

2B. Fees. Section 3.2 of the Agreement is deleted and replaced in its entirety with the following:

"3.2 Fees. The Company shall pay to the Consultant consulting fees of $75,000 per year, payable in equal quarterly installments. Payment for any partial quarter shall be prorated.

Transaction Bonus. If, within eighteen (18) months from the date hereof, the Company signs an agreement with a Partner (as defined below) encompassing a Qualifying Transaction (as defined below), the Company shall pay to the Consultant a cash bonus of $125,000 within fifteen (15) days of the signing of such agreement. For purposes of this Agreement, "Partner" means any third party for-profit entity. For purposes of this Agreement, "Qualifying Transaction" means a transaction pursuant to which the consideration received by the Company will, in the reasonable judgment of the Board of Directors of the Company, exceed $50 million within two (2) years from the date of the agreement with the Partner."

3. Full Force and Effect. Except as expressly provided in this First Amendment, all other terms, conditions and provisions of the Agreement shall continue in full force and effect as provided therein.

4. Entire Agreement. This First Amendment together with the Agreement constitute the full and complete agreement and understanding between Company and Consultant concerning the subject matter hereof.

IN WITNESS WHEREOF, Company and Consultant have caused this First Amendment to be executed by their duly authorized officer as of the Effective Date.

SYROS PHARMACEUTICALS, INC.

By: /s/ Nancy Simonian, M.D.
Nancy Simonian M.D.
CEO

CONSULTANT

By: /s/ Richard A. Young, Ph.D.
Richard A. Young, Ph.D.

CONSULTING AGREEMENT- SECOND AMENDMENT

This Second Amendment to the CONSULTING AGREEMENT (the "Second Amendment"), dated as of September 29, 2016 (the "Agreement Date") and effective as of July 3, 2016, is entered into by Syros Pharmaceuticals, Inc. (f/k/a LS22, Inc.), a Delaware corporation with its principal place of business at 620 Memorial Drive, Suite 300, Cambridge, MA 02139 (the "Company"), and Richard A. Young, Ph.D. (the "Consultant").

WHEREAS, the Company and the Consultant entered into a Consulting Agreement dated August 8, 2012 (the "Original Agreement");

WHEREAS, the parties entered into that certain First Amendment dated December 3, 2012 (the "First Amendment"; and the Original Agreement, as amended by the First Amendment, the "Agreement"), to amend the term of the Original Agreement and the compensation to the Consultant set forth therein; and

WHEREAS, the Company and the Consultant desire to further amend the term of the Agreement under Section 2 and the compensation set forth under Section 3 as described herein.

NOW THEREFORE, in consideration of the mutual covenants, conditions and agreements set forth herein, and for such other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties hereto agree as follows:

1. **Defined Terms.** Unless otherwise defined herein, the meaning of the terms used herein shall have the same meanings set forth in the Agreement.

2. **Amendments to Agreement.** The Company and the Consultant agree that the Agreement shall be and hereby is amended as follows:

a. Term. The reference to "July 3, 2016" in Section 2 of the Agreement shall be replaced by "July 3, 2019".

b. Equity Compensation. Section 3.1 of the Agreement shall be deleted and replaced in its entirety with the following:

"3.1 Equity Compensation. In consideration for the performance of the services hereunder, the Consultant has been awarded (a) a grant of 1,600,000 shares of restricted common stock, $0.001 par value per share, of the Company ("Common Stock"), having a purchase price of $0.001, pursuant to that certain Restricted Stock Agreement dated as of August 8, 2012 and (b) an option to purchase 75,000 shares of Common Stock, with an exercise price equal to the fair market value of such options on the date of grant, vesting upon certain performance-based milestones approved by the Board of Directors of the Company and having such other terms and conditions as shall be set forth in an option grant agreement between the Consultant and the Company."

c. Fees. Section 3.2 of the Agreement shall be deleted and replaced in its entirety with the following:

"3.2 Fees. The Company shall pay to the Consultant consulting fees of $125,000 per year, payable in equal quarterly installments. Payment for any partial quarter shall be prorated."

3. **Full Force and Effect.** Except as expressly provided in this Second Amendment, all other terms, conditions and provisions of the Agreement shall continue in full force and effect as provided therein.

4. **Entire Agreement.** This Second Amendment together with the Agreement constitute the full and complete agreement and understanding between the Company and the Consultant concerning the subject matter hereof.

[Remainder of page intentionally blank]

IN WITNESS WHEREOF, the Company and the Consultant have caused this Second Amendment to be executed by their duly authorized officer as of the Agreement Date.

SYROS PHARMACEUTICALS, INC.

By: /s/ Nancy Simonian, M.D.
Nancy Simonian M.D.
CEO

CONSULTANT

By: /s/ Richard A. Young, Ph.D.
Richard A. Young, Ph.D.

Exhibit 21.1

Subsidiaries of the Registrant

Syros Securities Corporation, a Massachusetts corporation and wholly-owned subsidiary of the Registrant.

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the Registration Statement (Form S-8 No. 333-212363) pertaining to the 2012 Equity Incentive Plan, 2016 Stock Incentive Plan, and 2016 Employee Stock Purchase Plan of Syros Pharmaceuticals, Inc. of our report dated March 20, 2017, with respect to the consolidated financial statements of Syros Pharmaceuticals, Inc., included in this Annual Report (Form 10-K) for the year ended December 31, 2016.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 20, 2017

Exhibit 31.1

CERTIFICATIONS

I, Nancy Simonian, certify that:

1. I have reviewed this Annual Report on Form 10-K of Syros Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 20, 2017

By: /s/ Nancy Simonian, M.D.
Nancy Simonian, M.D.
President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATIONS

I, Kyle D. Kuvalanka, certify that:

1. I have reviewed this Annual Report on Form 10-K of Syros Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 20, 2017

By: /s/ Kyle D. Kuvalanka
Kyle D. Kuvalanka
Chief Operating Officer
(Principal Financial and Accounting Officer)

Exhibit 32.1

**CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

In connection with the Annual Report on Form 10-K of Syros Pharmaceuticals, Inc. (the "Company") for the fiscal year ended December 31, 2016 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Nancy Simonian, President and Chief Executive Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to the best of her knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 20, 2017

By: /s/ Nancy Simonian, M.D.
Nancy Simonian, M.D.
President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 32.2

CERTIFICATION PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of Syros Pharmaceuticals, Inc. (the "Company") for the fiscal year ended December 31, 2016 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Kyle D. Kuvalanka, Chief Operating Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to the best of his knowledge:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 20, 2017

By: /s/ Kyle D. Kuvalanka
Kyle D. Kuvalanka
Chief Operating Officer
(Principal Financial and Accounting Officer)