



**8,667,333 Shares of Common Stock
Class A Warrants to Purchase 1,951,844 Shares of Common Stock**

We are offering 8,667,333 shares of common stock and Class A warrants to purchase 1,951,844 shares of common stock at an exercise price of \$8.625 per share of common stock (each a "Warrant"). The shares of common stock and Warrants will be sold in fixed combinations, with each one share of common stock that we sell in this offering being accompanied by 0.25 of a Warrant to purchase one share of common stock, except as may be otherwise elected by the purchasers thereof.

We are also offering the shares of common stock that are issuable from time to time upon exercise of the Warrants being offered by this prospectus supplement and accompanying prospectus.

There is no established public trading market for the Warrants, and we do not expect a market to develop. We do not intend to list the Warrants on the Nasdaq Global Select Market, any other national securities exchange or any other nationally recognized trading system. Without an active trading market, the liquidity of the Warrants will be limited.

Our common stock is listed on the Nasdaq Global Select Market under the symbol "SYRS." On April 4, 2019, the last reported sale price of our common stock on the Nasdaq Global Select Market was \$9.75 per share.

Each Warrant will be exercisable immediately, provided that the holder will be prohibited, subject to certain exceptions, from exercising the Warrant for shares of our common stock to the extent that immediately prior to or after giving effect to such exercise, the holder, together with its affiliates and other attribution parties, would own more than 4.99% of the total number of shares of our common stock then issued and outstanding, which percentage may be changed at the holders' election to a higher or lower percentage upon 61 days' notice to us. Each Warrant will expire 42 calendar months from the date of issuance. Investors who have agreed to purchase an aggregate of 859,957 shares of common stock have elected not to accept the Warrants (any such investor, an "opt-out investor"). Any opt-out investor will nevertheless pay the public offering price per share and accompanying Warrants set forth below.

Concurrently with this offering, and pursuant to a separate prospectus supplement, we are also conducting a public offering, or the Concurrent Offering, of 666 shares of our Series A convertible preferred stock, or the Series A preferred stock (and the shares of common stock issuable from time to time upon conversion of the Series A preferred stock) and Warrants to purchase 166,500 shares of common stock. Each share of Series A preferred stock is convertible into 1,000 shares of common stock.

	<i>Per Share and Accompanying Warrants</i>	<i>Total</i>
Public offering price	\$ 7.50	\$65,004,998
Underwriting discounts and commissions(1)	\$ 0.45	\$ 3,900,300
Proceeds, before expenses, to Syros Pharmaceuticals, Inc.	\$ 7.05	\$61,104,698

(1) We have agreed to reimburse the underwriters for certain FINRA-related expenses. See "Underwriting" beginning on page S-27 of this prospectus supplement.

Investing in our securities involves risks. See "[Risk factors](#)" beginning on page S-8 of this prospectus supplement, as well as those risk factors contained in the accompanying prospectus and the documents incorporated herein and therein.

Neither the Securities and Exchange Commission nor any other regulatory body has approved or disapproved of these securities or passed upon the accuracy or adequacy of this prospectus supplement or the accompanying prospectus. Any representation to the contrary is a criminal offense.

The underwriters expect to deliver the shares of common stock and Warrants to investors on or about April 9, 2019.

Joint Book-Running Managers

Cowen

Piper Jaffray

Lead Manager

JMP Securities

Co-Manager

Roth Capital Partners

April 5, 2019

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ABOUT THIS PROSPECTUS SUPPLEMENT

This document is in two parts. The first part is this prospectus supplement, which describes the specific terms of this offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference herein. The second part, the accompanying prospectus, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement and the information contained in the accompanying prospectus or any document incorporated by reference therein filed prior to the date of this prospectus supplement, you should rely on the information in this prospectus supplement; provided that if any statement in one of these documents is inconsistent with a statement in another document having a later date—for example, a document incorporated by reference in the accompanying prospectus—the statement in the document having the later date modifies or supersedes the earlier statement.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference herein were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

We and the underwriters have not authorized anyone to provide you with any information other than that contained in this prospectus supplement and the accompanying prospectus or in any free writing prospectus we may authorize to be delivered or made available to you. We and the underwriters take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We are offering to sell, and seeking offers to buy, our securities only in jurisdictions where offers and sales are permitted. The information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus is accurate only as of the date of this prospectus supplement, regardless of the time of delivery of this prospectus supplement or any sale of our securities. Our business, financial condition, results of operations and prospects may have changed since that date. You should also read and consider the information in the documents to which we have referred you in the sections entitled “Where you can find more information” and “Incorporation of certain documents by reference” in this prospectus supplement and in the accompanying prospectus.

For investors outside the United States: We and the underwriters have not done anything that would permit this offering or possession or distribution of this prospectus supplement and the accompanying prospectus in any jurisdiction where action for that purpose is required, other than in the United States. Persons outside the United States who come into possession of this prospectus supplement and the accompanying prospectus must inform themselves about, and observe any restrictions relating to, this offering and the distribution of this prospectus supplement and the accompanying prospectus outside the United States.

PROSPECTUS SUPPLEMENT SUMMARY

This summary does not contain all of the information that you should consider before investing in our securities. You should read this entire prospectus supplement and the accompanying prospectus carefully, including the consolidated financial statements and other information incorporated by reference in this prospectus supplement and the accompanying prospectus, before making an investment decision. In addition, please read the "Risk factors" section of this prospectus supplement beginning on page S-8 and the risk factors contained in our Annual Report on Form 10-K for the year ended December 31, 2018.

Overview

We are a biopharmaceutical company pioneering the understanding of the non-coding regulatory region of the genome to advance a new wave of medicines that control the expression of genes. We have built a proprietary platform that is designed to systematically and efficiently analyze this unexploited region of DNA 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 a range of diseases. We are currently focused on developing treatments for cancer and diseases resulting from mutations of a single gene, also known as monogenic diseases, and building a pipeline of gene control medicines.

Our lead product candidates are:

- SY-1425, a selective retinoic acid receptor alpha, or RAR α , agonist that is currently being evaluated in combination with azacitidine, a hypomethylating agent frequently used to treat acute myeloid leukemia, or AML, patients in a Phase 2 clinical trial in genomically defined subsets of patients with AML;
- SY-1365, a selective inhibitor of cyclin-dependent kinase 7, or CDK7, that is currently being evaluated in a Phase 1 clinical trial in patients with advanced solid tumors, including multiple ovarian and breast cancer patient populations as a single agent and in combination with standard-of-care therapies; and
- SY-5609, a novel CDK7 inhibitor that can be administered orally, which is being evaluated in investigational new drug application, or IND, enabling preclinical studies.

Our ongoing Phase 2 clinical trial is assessing the safety and efficacy of SY-1425 in combination with azacitidine in a cohort of approximately 25 newly diagnosed AML patients who are not suitable candidates for standard chemotherapy. All patients enrolled or to be enrolled in this cohort of the trial in support of our primary efficacy analyses have been or will be prospectively selected using our proprietary RARA or IRF8 biomarkers. In addition, to support the development of a commercial companion diagnostic test for SY-1425, we are evaluating SY-1425 in combination with azacitidine in a cohort of approximately 25 newly diagnosed AML patients who are not suitable candidates for standard chemotherapy and who are biomarker-negative.

At the American Society of Hematology Annual Meeting held in December 2018, or ASH 2018, we reported data from these cohorts of the Phase 2 clinical trial as of an October 29, 2018 data cut-off, and we continue to enroll and follow patients in the trial. As of the data cut-off, 11 biomarker-positive and eight biomarker-negative patients had been enrolled in the trial. Of the biomarker-positive patients, ten were evaluable for safety and eight were also evaluable for clinical responses. Of the biomarker-negative patients, seven were evaluable for safety and six were evaluable for clinical responses. We reported at ASH 2018 that SY-1425 in combination with azacitidine had been generally well-tolerated,

with no evidence of increased toxicities, and that adverse events had been consistent with what has previously been seen with SY-1425 and azacitidine as single agents in AML. We also reported that the aggregate rate of complete response and complete response with incomplete blood count recovery, as defined by Revised International Working Group, or IWG, criteria, as of the data cut-off was 50% and the overall response rate using IWG criteria was 63%, in each case in response-evaluable patients enrolled in the biomarker-positive cohort of the trial. Most of the initial responses reported were seen at the end of the first treatment cycle. Single-agent azacitidine has shown response rates of 18-29% in newly-diagnosed AML patients who are not suitable candidates for chemotherapy, with initial responses generally occurring after four cycles of treatment in most patients who respond. We also reported at ASH 2018 an overall response rate of 17% as of the data cut-off in response-evaluable patients enrolled in the biomarker-negative cohort. While data from this cohort are less mature (because enrollment in this cohort started later than the biomarker-positive cohort), we believe that the difference in the observed overall response rates as of the cut-off date supports the potential predictive value of the RARA and IRF8 biomarkers for identifying patients most likely to respond to SY-1425. We expect to complete enrollment in the biomarker-positive cohort of the trial in mid-2019 and to report updated clinical data in the second half of 2019. We also plan to expand this trial in the third quarter of 2019 to include an assessment of the safety and efficacy of SY-1425 in combination with azacitidine in approximately 25 biomarker-positive patients with relapsed or refractory AML and expect to report initial data on these patients in 2020.

We also reported data at ASH 2018 from a pilot cohort of our Phase 2 clinical trial of SY-1425 evaluating the safety and efficacy of SY-1425 in combination with daratumumab, an anti-CD38 antibody approved for the treatment of multiple myeloma, in biomarker-positive patients with relapsed or refractory AML or higher-risk myelodysplastic syndrome, or MDS. Specifically, we reported that SY-1425 in combination with daratumumab was generally well tolerated with no evidence of increased toxicities, and that, while eight of nine evaluable patients had increased CD38 expression in myeloid blast cells, this expression increased to levels exceeding those of a multiple myeloma cell line in only two of those patients. In January 2019, we reported that we made a portfolio prioritization decision not to pursue further development of SY-1425 in combination with daratumumab beyond completion of this pilot cohort, which is closed to further enrollment.

In September 2018, we opened the expansion portion of our Phase 1 clinical trial evaluating the safety and clinical activity of SY-1365 in multiple ovarian cancer populations as a single agent as well as in combination with carboplatin, a chemotherapeutic agent, following completion of the dose-escalation portion of the trial. The high-grade serous ovarian cancer populations being evaluated include a 24-patient cohort evaluating SY-1365 as a single agent in patients who have relapsed after three or more prior therapies and a 24-patient cohort evaluating SY-1365 in combination with carboplatin in patients who relapsed after one or more prior therapies but who may still benefit from additional platinum-based treatment. We expect that a new 12-patient pilot cohort evaluating SY-1365 as a single agent in patients with recurrent ovarian clear cell cancer will be open for enrollment in the second quarter of 2019. We have stopped enrollment in a previously announced pilot cohort evaluating SY-1365 in patients with primary platinum-refractory ovarian cancer due to the recent approval of a new therapy in this indication that we believe will result in fewer patients meeting the strict clinical definition of "primary platinum refractory." We are also evaluating SY-1365 in combination with fulvestrant, a hormonal medicine, in approximately 12 patients with hormone-receptor positive, or HR+, HER2-negative metastatic breast cancer who have previously been treated with a CDK4/6 inhibitor plus an aromatase inhibitor. In addition, we are evaluating the mechanism of action of SY-1365 as a single agent in approximately 30 patients with any solid tumor accessible for biopsy. We plan to report initial clinical data from the expansion portion of our Phase 1 clinical trial in the fourth quarter of 2019. We expect these data to include initial safety assessments from the cohort evaluating SY-1365 in

combination with carboplatin, as well as initial safety and efficacy assessments from the cohort evaluating SY-1365 in patients who have relapsed after three or more prior therapies and in patients with any solid tumor accessible for biopsy. We expect to report initial data from the other cohorts of the trial, including the recurrent ovarian clear cell cancer cohort, in 2020.

In November 2018, we reported data as of October 15, 2018 from the dose-escalation portion of the Phase 1 clinical trial of SY-1365 at the EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium, or ENA 2018, which demonstrated proof-of mechanism at tolerable doses in patients with advanced solid tumors. Specifically, we reported that SY-1365 demonstrated dose-dependent effects on CDK7 occupancy and downstream gene expression changes in blood cells. In addition, we reported that adverse events occurring in the dose-escalation portion of the trial were predominantly low-grade, reversible and generally manageable and that a maximum tolerated dose was not defined. We also reported that clinical activity per Response Evaluation Criteria in Solid Tumors 1.1, or RECIST, criteria was observed in seven of the 19 patients (37%) who were evaluable for clinical responses, including one patient with recurrent ovarian clear cell cancer in her fourth relapse who had a confirmed partial response after two cycles of treatment at an 80 mg/m² twice weekly dose. This patient remained in a partial response at an assessment after six cycles of treatment. Six additional patients had stable disease lasting between 50 and 127 days. Most of these patients received doses of SY-1365 equal to or greater than 32 mg/m². Based on these data, we initiated the expansion cohorts of the Phase 1 clinical trial at 53 and 80 mg/m², and we are exploring once and twice weekly treatment regimens.

In November 2018, we designated SY-5609 as a development candidate to enter IND-enabling preclinical studies. We expect to complete these studies during 2019 in order to support potential initiation of a Phase 1 clinical trial of SY-5609 in oncology patients in early 2020.

We currently have several other programs in our preclinical and discovery pipeline, including a CDK12/13 inhibitor program, a program directed to inhibitors of a macrophage target in immuno-oncology, and discovery programs related to a gene control target to treat sickle cell disease and in the field of cancer. We have and are continuing to use our gene control platform in collaboration with third parties to identify and validate targets in diseases beyond our current areas of focus. To this end, we entered into a target discovery, research collaboration and option agreement with Incyte Corporation, or Incyte, in January 2018 under which we are using our platform to identify novel therapeutic targets with a focus on myeloproliferative neoplasms.

Risks associated with our business

Our business is subject to a number of risks of which you should be aware before making an investment decision. These risks are discussed more fully in the "Risk factors" section of our Annual Report on Form 10-K for the year ended December 31, 2018. These risks include the following:

- 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 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 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.

- 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.
- Our gene control platform may fail to help us discover and develop additional potential product candidates.
- In the near term, we are dependent on the success of SY-1425, SY-1365 and SY-5609. If we are unable to initiate or complete the clinical development of, obtain marketing approval for or successfully commercialize SY-1425, SY-1365 or SY-5609, either alone or with a collaborator, or if we experience significant delays in doing so, our business could be substantially harmed.
- If clinical trials of any product candidates that we, or any future collaborators, may develop fail to satisfactorily demonstrate safety and efficacy to the U.S. Food and Drug Administration, or 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.
- 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.
- 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.
- 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.
- 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 corporate information

We were incorporated under the laws of the State of Delaware on November 9, 2011 under the name LS22, Inc. Our executive offices are located at 620 Memorial Drive, Suite 300, Cambridge, Massachusetts 02139, and our telephone number is (617) 744-1340. Our website address is www.syros.com. The information contained on, or that can be accessed through, our website is not a part of this prospectus supplement. We have included our website address in this prospectus supplement solely as an inactive textual reference.

Except as otherwise indicated herein or as the context otherwise requires, references in this prospectus supplement to “Syros,” “the company,” “we,” “us” and “our” refer to Syros Pharmaceuticals, Inc. and its wholly owned subsidiaries.

The Syros logo, “Syros” and “Syros Pharmaceuticals” are our trademarks. Solely for convenience, the trademarks and trade names in this prospectus supplement are referred to without the ® and ™ symbols, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto. The trademarks, trade names and service marks appearing in this prospectus supplement are the property of their respective owners.

Concurrent offering of shares of Series A preferred stock and Class A warrants to purchase common stock

Concurrently with this offering, we are conducting a public offering of 666 shares of our Series A preferred stock (and the 666,000 shares of common stock issuable from time to time upon conversion of the Series A preferred stock), and Warrants to purchase 166,500 shares of common stock, which we refer to as the Concurrent Offering. The Concurrent Offering is being conducted as a separate public offering by means of a separate prospectus supplement. This offering is not contingent upon the completion of the Concurrent Offering and the Concurrent Offering is not contingent upon the completion of this offering. We cannot assure you that either or both of the offerings will be completed.

THE OFFERING

Common stock offered by us pursuant to this prospectus supplement	8,667,333 shares of common stock. This prospectus supplement also relates to the offering of the shares of our common stock issuable upon exercise of the Warrants, as discussed below.
Warrants offered by us pursuant to this prospectus supplement	Warrants to purchase 1,951,844 shares of common stock. Each Warrant will have an exercise price per share of common stock of \$8.625 and will expire 42 calendar months from the date of issuance. Each Warrant will be immediately exercisable, provided that the holder will be prohibited, subject to certain exceptions, from exercising the Warrant for shares of our common stock to the extent that immediately prior to or after giving effect to such exercise, the holder, together with its affiliates and other attribution parties, would own more than 4.99% of the total number of shares of our common stock then issued and outstanding, which percentage may be changed at the holders' election to a higher or lower percentage upon 61 days' notice to us. This prospectus supplement also relates to the offering of the shares of our common stock issuable upon exercise of the Warrants.
Common stock to be outstanding after this offering	42,433,197 shares of common stock, assuming no exercise of the Warrants included in this offering or in the Concurrent Offering.
Use of proceeds	We intend to use the net proceeds from this offering and the Concurrent Offering to fund the development of our ongoing clinical and preclinical programs, and for working capital and other general corporate purposes. See "Use of proceeds" for more information.
Risk factors	You should read the "Risk factors" beginning on page S-8 and the risk factors contained in our Annual Report on Form 10-K for the year ended December 31, 2018, as well as the other information included in, or incorporated by reference into, this prospectus supplement and the accompanying prospectus for a discussion of factors to consider carefully before deciding to invest in our securities.

Concurrent offering

Concurrently with this offering, we are conducting a public offering of 666 shares of our Series A preferred stock (and the 666,000 shares of common stock issuable from time to time upon conversion of the Series A preferred stock), and Warrants to purchase 166,500 shares of common stock. The Concurrent Offering is being conducted as a separate public offering by means of a separate prospectus supplement. This offering is not contingent upon the completion of the Concurrent Offering, and the Concurrent Offering is not contingent upon the completion of this offering.

Nasdaq Global Select Market symbol

Our common stock is listed on the Nasdaq Global Select Market under the symbol "SYRS." There is no established public trading market for the Warrants, and we do not expect a market to develop. We do not intend to apply for listing of the Warrants on any securities exchange or other nationally recognized trading system. Without an active trading market, the liquidity of the Warrants will be limited. See "Description of securities we are offering" for additional information.

The number of shares of our common stock to be outstanding after this offering is based on 33,765,864 shares of our common stock outstanding as of December 31, 2018 and excludes:

- 3,732,643 shares of common stock issuable upon exercise of stock options outstanding as of December 31, 2018 at a weighted-average exercise price of \$9.88 per share;
- 2,836,921 shares of common stock reserved as of December 31, 2018 for future issuance under our 2016 Stock Incentive Plan;
- 1,084,756 shares of common stock reserved as of December 31, 2018 for future issuance under our 2016 Employee Stock Purchase Plan; and
- 666,000 shares of common stock issuable upon conversion of Series A preferred stock being offered by us in connection with the Concurrent Offering.

Unless otherwise indicated, this prospectus supplement reflects and assumes the following:

- no exercise of the outstanding stock options described above; and
- no exercise of the Warrants included in this offering or in the Concurrent Offering.

In addition, we may in the future sell additional shares of our common stock pursuant to the sales agreement with Cowen and Company, LLC. As of the date of this prospectus supplement, \$32.8 million of common stock remains available for sale under the Sales Agreement, which common stock may be sold by us after the expiration or waiver of the 60-day lock-up period applicable to us and described under the section of this prospectus supplement entitled "Underwriting."

RISK FACTORS

An investment in our securities involves risks. You should carefully consider the following risk factors, as well as the risk factors included in our Annual Report on Form 10-K for the year ended December 31, 2018, together with all of the other information included in, or incorporated by reference into, this prospectus supplement and the accompanying prospectus in evaluating an investment in our securities. If any of the following risks were to occur, our business, financial condition or results of operations could be materially adversely affected. In that case, the trading price of our common stock (including the common stock issuable upon exercise of the Warrants issued in this offering) could decline and you could lose all or part of your investment.

Risks related to our securities and this offering

Following this offering, our executive officers, directors and principal stockholders will continue to own a significant percentage of our stock and will be able to substantially influence matters submitted to stockholders for approval.

Upon completion of this offering, 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, will continue to beneficially own a significant percentage of our common stock. As a result, if these stockholders were to choose to act together, they would be able to substantially influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, could significantly influence the election of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. This concentration of voting power could delay or prevent an acquisition of our company on terms that you may desire.

If you purchase securities in this offering, you will suffer immediate dilution of your investment.

The public offering price of our common stock and the accompanying Class A Warrants is substantially higher than the as adjusted net tangible book value per share of our common stock after this offering. Therefore, if you purchase securities in this offering, you will pay an effective price per share of common stock that substantially exceeds our as adjusted net tangible book value per share after giving effect to this offering. If you purchase securities in this offering, assuming no exercise of the Warrants included in this offering, no value is attributed to such Warrants and such Warrants are classified as and accounted for as equity, you will experience immediate and substantial dilution in net tangible book value of \$4.22 per share, after giving effect to this offering. In the event Warrants are exercised by holders, you will experience additional dilution to the extent that the exercise price of those Warrants is higher than the book value per share of our common stock. Furthermore, if previously issued options to acquire common stock are exercised at prices below the public offering price of our common stock and the accompanying Warrants, or the Warrants are accounted for as liabilities, you will experience further dilution.

There is no public market for the Warrants being offered by us in this offering.

There is no established public trading market for the Warrants being offered in this offering, and we do not expect a market to develop. In addition, we do not intend to apply to list the Warrants on any national securities exchange or other nationally recognized trading system, including the Nasdaq Global Select Market. Without an active market, the liquidity of the Warrants will be limited.

Except for the right to participate in certain dividends and distributions, holders of Warrants purchased in this offering will have no rights as common stockholders until such holders exercise their Warrants and acquire our common stock.

Until holders of Warrants acquire shares of our common stock upon exercise thereof, except for the right to participate in certain dividends and distributions, such holders will have no rights with respect to the shares of our common stock underlying the Warrants. Upon exercise of the Warrants, the holders will be entitled to exercise the rights of a common stockholder only as to matters for which the record date occurs after the exercise date.

The Warrants are speculative in nature.

The Warrants only represent the right to acquire shares of common stock at a fixed price for a limited period of time. Specifically, commencing on the date of issuance, holders of the Warrants may exercise their right to acquire the common stock and pay an exercise price per share of \$8.625, subject to certain adjustments, prior to 42 calendar months from the date of issuance, after which date any unexercised Warrants will expire and have no further value. Moreover, following this offering, the market value of the Warrants, if any, is uncertain and there can be no assurance that the market value of the Warrants will equal or exceed their imputed offering price. The Warrants will not be listed or quoted for trading on any market or exchange. There can be no assurance that the market price of the common stock will ever equal or exceed the exercise price of the Warrants, and consequently, it may not ever be profitable for holders of the Warrants to exercise the Warrants.

We have broad discretion in the use of the net proceeds from this offering and the Concurrent Offering and may not use them effectively.

Our management will have broad discretion in the application of the net proceeds from this offering and the Concurrent Offering and could spend the proceeds in ways that do not improve our results of operations or enhance the value of our securities. The failure by our management to apply these funds effectively could result in financial losses, and these financial losses could have a material adverse effect on our business, cause the price of our securities to decline and delay the development of our product candidates. Pending their use, we may invest the net proceeds from this offering and the Concurrent Offering in a manner that does not produce income or that loses value.

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

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

In addition, we entered into a sales agreement, with Cowen and Company, LLC, as agent, in July 2017, which we refer to as the Sales Agreement, under which we may issue and sell from time to time through Cowen and Company, LLC shares of our common stock, in an aggregate amount not to exceed \$50 million. As of the date of this prospectus supplement, \$32.8 million of common stock remains available for sale under the Sales Agreement, which common stock may be sold by us after the expiration or waiver of the 60-day lock-up period applicable to us and described under the section of this prospectus supplement entitled "Underwriting." To the extent that we sell additional shares of our common stock pursuant to the Sales Agreement, investors purchasing securities in this offering could experience further dilution.

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

Sales of substantial amounts of our common stock in the public markets, or the perception that such sale might occur, could reduce the price that our common stock might otherwise attain.

Sales of a substantial amount of shares of our common stock in the public market, particularly sales by our directors, executive officers and significant stockholders, or the perception that these sales could occur, could cause the market price of our common stock to decline and may make it more difficult for you to sell your securities at a time and price that you deem appropriate.

As of December 31, 2018, we had 33,765,864 shares of common stock outstanding. The holders of a significant percentage of the outstanding shares of our common stock have rights, subject to specified 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. We have also registered all shares of common stock that we may issue under our equity compensation plans. As a result, these shares can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and the lock-up agreements described below, to the extent applicable.

Our executive officers and directors and certain of our significant stockholders have entered into lock-up agreements with the underwriters under which they have agreed, subject to specific exceptions, not to sell, directly or indirectly, any shares of common stock without the permission of Cowen and Company, LLC and Piper Jaffray & Co. for a period of 60 days following the date of this prospectus supplement. We refer to such period as the lock-up period. When the lock-up period expires or if the lock-up restrictions are waived, which Cowen and Company, LLC and Piper Jaffray & Co. may do at any time with respect to all or a portion of the securities subject to such restrictions in their sole discretion, we and the stockholders who are subject to lock-up agreements will be able to sell shares in the public market. Sales of a substantial number of such shares upon expiration of the lock-up agreements, the perception that such sales may occur, or early release of these agreements, could cause the market price of our common stock to fall or make it more difficult for you to sell your securities at a time and price that you deem appropriate.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS AND INDUSTRY DATA

This prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein contain forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this prospectus supplement, the accompanying prospectus or the documents incorporated by reference herein and therein, 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 prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein are based upon information available to us as of the date such statements are made and, while we believe such information forms a reasonable basis for such statements at the time made, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information.

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

- our plans to initiate and expand clinical trials of our product candidates and our expectations for the timing, quantity and quality of information to be reported from our clinical trials of SY-1425 and SY-1365;
- our plans to progress SY-5609 through IND-enabling preclinical studies and initiate clinical development;
- planned clinical trials for our product candidates, whether conducted by us or by any future collaborators, including the timing of these trials and of the anticipated results;
- our plans to research, develop, manufacture and commercialize our current and future product candidates;
- our plans to develop and seek approval of companion diagnostic tests for use in identifying patients who may benefit from treatment with our products and product candidates;
- our expectations regarding the potential benefits of our gene control platform and our approach;
- our ability to enter into, and the terms and timing of, any collaborations, license agreements, or other arrangements;
- whether our collaboration with Incyte will yield any validated targets, whether Incyte will exercise any of its options to exclusively license intellectual property directed to such targets, and whether and when any of the target validation fees, option exercise fees, milestone payments or royalties under the Incyte collaboration will ever be paid;
- the potential benefits of any future collaboration;
- developments relating to our competitors and our industry;
- the impact of government laws and regulations;
- 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;

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- 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 expectations related to the use of proceeds from this offering and the Concurrent Offering;
- the successful completion of the Concurrent Offering; and
- our estimates regarding expenses, future revenue, capital requirements and need for additional financing.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. New risks and uncertainties emerge from time to time, and it is not possible for us to predict all risks and uncertainties that could have an impact on the forward-looking statements contained or incorporated by reference in this prospectus supplement and the accompanying prospectus. We have included important factors in the cautionary statements included or incorporated by reference in this prospectus supplement and the accompanying prospectus, particularly in the "Risk factors" section of this prospectus supplement and those listed under the caption "Risk factors" in our most recent Annual Report on Form 10-K and other filings we make with the SEC, 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 prospectus supplement, the accompanying prospectus and the documents incorporated by reference herein and therein and the documents that we have filed as exhibits to the registration statement of which this prospectus supplement is a part 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 prospectus supplement and the accompanying prospectus includes and incorporates by reference certain 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 or incorporated by reference in this prospectus supplement and the accompanying prospectus 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 of this prospectus supplement and those listed under the caption "Risk factors" in our most recent Annual Report on Form 10-K and other filings we make with the SEC. These and other factors could cause results to differ materially from those expressed in the estimates made by the independent parties and by us.

In addition, statements that "we believe" and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this prospectus supplement or of the documents incorporated by reference herein, as applicable, 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 statements are inherently uncertain and investors are cautioned not to unduly rely upon these statements.

USE OF PROCEEDS

We estimate that the net proceeds to us from this offering will be approximately \$60.7 million, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us. This estimate excludes the proceeds, if any, from exercise of the Warrants sold in this offering.

In addition, we estimate that the net proceeds to us from the Concurrent Offering will be approximately \$4.7 million after deducting underwriting discounts and commissions and estimated offering expenses payable by us. This offering is not contingent upon the completion of the Concurrent Offering, and the Concurrent Offering is not contingent upon the completion of this offering.

If all of the Warrants sold in this offering and the Concurrent Offering were to be exercised in cash, we would receive additional net proceeds of approximately \$18.3 million. We cannot predict when or if the Warrants will be exercised. It is possible that the Warrants may expire and may never be exercised.

We intend to use the net proceeds from this offering and the Concurrent Offering to fund the development of our ongoing clinical and preclinical programs, and for working capital and other general corporate purposes. Based on our current plans, we believe our existing cash and cash equivalents, together with the net proceeds to us from this offering and the Concurrent Offering, will be sufficient to fund our operations into 2021.

This expected use of net proceeds from this offering and the Concurrent Offering represents our intentions based upon our current plans and business conditions, which could change in the future as our plans and business conditions evolve. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development, the status of, and results from, preclinical studies and clinical trials, the potential need to conduct additional clinical trials to obtain approval of our product candidates for all intended indications, as well as any additional collaborations that we may enter into with third parties for our product candidates and any unforeseen cash needs. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering and the Concurrent Offering.

Pending use of the proceeds as described above, we intend to invest the proceeds in short-term, interest-bearing, investment-grade securities.

CAPITALIZATION

The following table sets forth our consolidated cash, cash equivalents and marketable securities and our capitalization as of December 31, 2018, as follows:

- on an actual basis; and
- on an as adjusted basis to reflect the issuance and sale in this offering of 8,667,333 shares of our common stock and Warrants to purchase 1,951,844 shares of our common stock at a public offering price of \$7.50 per share of common stock and the accompanying Warrant, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, and assuming no exercise of the Warrants offered hereby, and that no value is attributed to such Warrants and such Warrants are classified and accounted for as equity.

You should read the following table together with “Description of Capital Stock” appearing in the accompanying prospectus, and our consolidated financial statements and related notes to those statements and the “Management’s Discussion and Analysis of Financial Condition and Results of Operations” in our Annual Report on Form 10-K for the year ended December 31, 2018, which are incorporated by reference in this prospectus supplement.

(in thousands, except share data)	As of December 31, 2018	
	Actual	As adjusted
Cash, cash equivalents and marketable securities	\$ 99,679	\$ 160,414
Common stock, par value \$0.001 per share: 200,000,000 shares authorized, actual and as adjusted; 33,765,864 shares issued and outstanding, actual; 42,433,197 shares issued and outstanding, as adjusted	\$ 34	\$ 43
Additional paid-in capital	296,100	356,826
Accumulated other comprehensive loss	(3)	(3)
Accumulated deficit	(217,545)	(217,545)
Total stockholders’ equity	78,586	139,321
Total capitalization	\$ 78,586	\$ 139,321

The table above does not include:

- 3,732,643 shares of common stock issuable upon exercise of stock options outstanding as of December 31, 2018 at a weighted-average exercise price of \$9.88 per share;
- 2,836,921 shares of common stock reserved as of December 31, 2018 for future issuance under our 2016 Stock Incentive Plan;
- 1,084,756 shares of common stock reserved as of December 31, 2018 for future issuance under our 2016 Employee Stock Purchase Plan;
- 666 shares of Series A preferred stock being offered in the Concurrent Offering;
- 666,000 shares of common stock issuable upon conversion of the Series A preferred stock being offered by us in the Concurrent Offering; and
- 2,118,344 shares of common stock issuable upon exercise of the Warrants being offered by us in this offering or the Concurrent Offering.

DILUTION

If you invest in our securities in this offering, your ownership interest will be diluted to the extent of the difference between the public offering price per share of common stock and the accompanying Warrants and the as adjusted net tangible book value per share of our common stock immediately after this offering.

Our net tangible book value as of December 31, 2018 was \$78.6 million, or \$2.33 per share of common stock based upon 33,765,864 shares outstanding. Net tangible book value per share is equal to our total tangible assets less our total liabilities, divided by the total number of shares of common stock outstanding as of December 31, 2018.

After giving effect to our issuance and sale of 8,667,333 shares of common stock and Warrants to purchase 1,951,844 shares of common stock in this offering at the public offering price per share of common stock and the accompanying Warrants of \$7.50, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us, and assuming no exercise of the Warrants offered hereby, and that no value is attributed to such Warrants and that such Warrants are classified as and accounted for as equity, our net tangible book value as of December 31, 2018 would have been \$139.3 million, or \$3.28 per share. This represents an immediate increase in net tangible book value of \$0.96 per share to existing stockholders and an immediate dilution in net tangible book value of \$4.22 per share to investors participating in this offering.

The following table illustrates this dilution on a per share basis:

Public offering price per share of common stock and the accompanying Warrants	\$7.50
Net tangible book value per share of common stock as of December 31, 2018	\$2.33
Increase in net tangible book value per share of common stock attributable to new investors in this offering	<u>\$0.96</u>
Net tangible book value per share of common stock as of December 31, 2018 after giving effect to this offering	<u>\$3.28</u>
Dilution in net tangible book value per share of common stock to new investors in this offering	<u><u>\$4.22</u></u>

The table above is based on 33,765,864 shares of common stock outstanding as of December 31, 2018 and does not include:

- 3,732,643 shares of common stock issuable upon exercise of stock options outstanding as of December 31, 2018 at a weighted-average exercise price of \$9.88 per share;
- 2,836,921 shares of common stock reserved as of December 31, 2018 for future issuance under our 2016 Stock Incentive Plan;
- 1,084,756 shares of common stock reserved as of December 31, 2018 for future issuance under our 2016 Employee Stock Purchase Plan;
- 666,000 shares of common stock issuable upon conversion of Series A preferred stock being offered by us in connection with the Concurrent Offering; and
- 2,118,344 shares of common stock issuable upon exercise of the Warrants being offered by us in this offering or the Concurrent Offering.

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The above discussion and table do not take into account giving effect to the shares of Series A preferred stock and accompanying Warrants offered by us in the Concurrent Offering. Giving effect to both this offering and the Concurrent Offering at the public offering price per share of Series A preferred stock and the accompanying Warrants of \$7,500 (assuming conversion of all shares of Series A preferred stock offered in the Concurrent Offering, and assuming no exercise of the Warrants, and that no value is attributed to such Warrants and such Warrants are classified as and accounted for as equity), our as adjusted net tangible book value as of December 31, 2018 would have been approximately \$144.0 million, or \$3.34 per share of common stock, which represents an immediate increase in net tangible book value of \$1.01 per share of common stock to existing stockholders and immediate dilution in net tangible book value of \$4.16 per share of common stock to new investors participating in this offering.

To the extent that any options are exercised, new equity awards are granted under our equity incentive plans, additional shares of common stock are issued pursuant to the Sales Agreement with Cowen and Company, LLC, the Warrants issued in this offering, or the Concurrent Offering, are accounted for as liabilities or we otherwise issue additional shares of common stock or warrants in the future, there will be further dilution to new investors.

DIVIDEND POLICY

We have never declared or paid any cash dividends on our capital stock. We currently plan to retain future earnings, if any, to finance the operation, development and growth 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.

DESCRIPTION OF SECURITIES WE ARE OFFERING

We are offering 8,667,333 shares of our common stock and Warrants to purchase 1,951,844 shares of our common stock. We are also registering the shares of common stock issuable from time to time upon exercise of Warrants offered hereby.

Common Stock

Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. An election of directors by our stockholders is determined by a plurality of the votes cast by the stockholders entitled to vote on the election. Other matters are decided by the affirmative vote of our stockholders having a majority in voting power of the votes cast by the stockholders present or represented and voting on such matter, except as otherwise disclosed below. Holders of common stock are entitled to receive proportionately any dividends as may be declared by our board of directors, subject to any preferential dividend rights of outstanding preferred stock.

In the event of our liquidation or dissolution, the holders of common stock are entitled to receive proportionately all assets available for distribution to stockholders after the payment of all debts and other liabilities and subject to the prior rights of any outstanding preferred stock. Holders of common stock have no preemptive, subscription, redemption or conversion rights. The rights, preferences and privileges of holders of common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future.

Additional information regarding our capital stock, including a description of certain terms of our certificate of incorporation and bylaws and applicable provisions of Delaware corporate law, is set forth under the caption "Description of Capital Stock" starting on page 19 of the accompanying prospectus.

Warrants

The following summary of certain terms and provisions of the Warrants is not complete and is subject to, and qualified in its entirety by, the provisions of the Warrants. Prospective investors should carefully review the terms and provisions of the form of Warrant that is filed as an exhibit to the registration statement of which this prospectus supplement forms a part for a complete description of the terms and conditions of the Warrants.

Duration and Exercise Price. Each Warrant will have an initial exercise price per share equal to \$8.625 per share of our common stock. The Warrants will be immediately exercisable and will expire 42 calendar months from the date of issuance. The exercise price and number of shares of common stock issuable upon exercise is subject to appropriate adjustment in the event of stock dividends, stock splits, reorganizations or similar events affecting our common stock and the exercise price. The Warrants will be issued separately from the common stock included in this offering.

Cashless Exercise. If, at the time a holder exercises its Warrants, a registration statement registering the issuance of the shares of common stock underlying the Warrants under the Securities Act is not then effective or available for the issuance of such shares, then in lieu of making the cash payment otherwise contemplated to be made to us upon such exercise in payment of the aggregate exercise price, the holder may elect instead to receive upon such exercise (either in whole or in part) the net number of shares of common stock determined according to a formula set forth in the Warrants.

Exercisability. The Warrants will be exercisable, at the option of each holder, in whole or in part, by delivering to us a duly executed exercise notice accompanied by payment in full for the number of shares of our common stock purchased upon such exercise. A holder (together with its affiliates and

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other attribution parties) may not exercise any portion of a Warrant to the extent that immediately prior to or after giving effect to such exercise the holder would own more than 4.99% of the outstanding common stock immediately after exercise, which percentage may be changed at the holder's election to a higher or lower percentage upon 61 days' notice to us.

Fractional Shares. No fractional shares of common stock will be issued upon the exercise of the Warrants. Rather, the number of shares of common stock to be issued will be rounded to the nearest whole number.

Transferability. Subject to applicable laws, a Warrant may be transferred at the option of the holder upon surrender of the Warrant to us together with the appropriate instruments of transfer.

Exchange Listing. We do not intend to list the Warrants on any securities exchange or nationally recognized trading system. The common stock issuable upon exercise of the Warrants is currently listed on the Nasdaq Global Select Market.

Rights as a Stockholder. Except for the right to participate in certain dividends and distributions or by virtue of such holder's ownership of shares of our common stock, the holders of the Warrants do not have the rights or privileges of holders of our common stock, including any voting rights, until they exercise their Warrants.

Fundamental Transaction. In the event of a fundamental transaction, as described in the Warrants and generally including any reorganization, recapitalization or reclassification of our common stock, the sale, transfer or other disposition of all or substantially all of our properties or assets, our consolidation or merger with or into another person, the acquisition of at least 50% of our outstanding common stock, or any person or group becoming the beneficial owner of at least 50% of the voting power represented by our outstanding common stock, the holders of the Warrants will be entitled to receive upon exercise of the Warrants the kind and amount of securities, cash or other property that the holders would have received had they exercised the Warrants immediately prior to such fundamental transaction. In addition, in the event of a fundamental transaction which is approved by our Board, the holders of the Warrants have the right to require us or a successor entity to redeem the Warrants for cash in the amount of the Black-Scholes value of the unexercised portion of the Warrants on the date of the consummation of the fundamental transaction. In the event of a fundamental transaction which is not approved by our Board, the holders of the Warrants have the right to require us or a successor entity to redeem the Warrants for the consideration paid in the fundamental transaction in the amount of the Black-Scholes value of the unexercised portion of the Warrants on the date of the consummation of the fundamental transaction payable at our option in either shares of our common stock (or, in certain cases, in the securities of the successor entity) or cash.

Listing on the Nasdaq Global Select Market

Our common stock is listed on the Nasdaq Global Select Market under the trading symbol "SYRS." There is no established public trading market for the Warrants, and we do not expect a market to develop. We do not intend to list the Warrants on the Nasdaq Global Select Market, any other national securities exchange or any other nationally recognized trading system.

Transfer Agent and Registrar

The transfer agent and registrar for shares of our common stock (including the underlying shares of common stock issuable upon exercise of the Warrants) is Computershare Trust Company, N.A.

Warrant Agent

Our warrant agent is Computershare Trust Company, N.A.

MATERIAL U.S. FEDERAL TAX CONSIDERATIONS FOR HOLDERS OF OUR COMMON STOCK AND WARRANTS

The following discussion describes the material U.S. federal income tax consequences of the acquisition, ownership and disposition of our common stock and Warrants acquired in this offering. This discussion is based on the current provisions of the Internal Revenue Code of 1986, as amended, referred to as the Code, existing and proposed U.S. Treasury regulations promulgated thereunder, and administrative rulings and court decisions in effect as of the date hereof, all of which are subject to change at any time, possibly with retroactive effect. No ruling has been or will be sought from the Internal Revenue Service, or IRS, with respect to the matters discussed below, and there can be no assurance the IRS will not take a contrary position regarding the tax consequences of the acquisition, ownership or disposition of our common stock or Warrants, or that any such contrary position would not be sustained by a court.

We assume in this discussion that the shares of our common stock and Warrants will be held as capital assets (generally, property held for investment). This discussion does not address all aspects of U.S. federal income taxes, does not discuss the potential application of the Medicare contribution tax or the alternative minimum tax and does not address state or local taxes or U.S. federal gift and estate tax laws, except as specifically provided below with respect to non-U.S. holders, or any non-U.S. tax consequences that may be relevant to holders in light of their particular circumstances. This discussion also does not address the special tax rules applicable to particular holders, such as:

- financial institutions;
- brokers or dealers in securities;
- tax-exempt organizations;
- pension plans;
- regulated investment companies;
- owners that hold our common stock or Warrants as part of a straddle, hedge, conversion transaction, synthetic security or other integrated investment;
- insurance companies;
- controlled foreign corporations, passive foreign investment companies, or corporations that accumulate earnings to avoid U.S. federal income tax; and
- certain U.S. expatriates.

In addition, this discussion does not address the tax treatment of partnerships or other pass-through entities or persons who hold our common stock or Warrants through partnerships or other entities which are pass-through entities for U.S. federal income tax purposes. A partner in a partnership or other pass-through entity that will hold our common stock or Warrants should consult his, her or its own tax advisor regarding the tax consequences of the ownership and disposition of our common stock or Warrants through a partnership or other pass-through entity, as applicable.

This discussion of U.S. federal income tax considerations is for general information purposes only and is not tax advice. Prospective investors should consult their own tax advisors regarding the U.S. federal, state, local and non-U.S. income and other tax considerations of acquiring, holding and disposing of our common stock and Warrants.

For the purposes of this discussion, a "U.S. Holder" means a beneficial owner of our common stock or Warrants that is for U.S. federal income tax purposes (a) an individual citizen or resident of the United States, (b) a corporation (or other entity taxable as a corporation for U.S. federal income tax purposes), created or organized in or under the laws of the United States, any state thereof or the District of Columbia, (c) an estate the income of which is subject to U.S. federal income taxation

regardless of its source, or (d) a trust if it (1) is subject to the primary supervision of a court within the United States and one or more U.S. persons (within the meaning of Section 7701(a)(30) of the Code) has the authority to control all substantial decisions of the trust or (2) has a valid election in effect under applicable U.S. Treasury regulations to be treated as a U.S. person. A "Non-U.S. Holder" is, for U.S. federal income tax purposes, a beneficial owner of common stock or Warrants that is not a U.S. Holder or a partnership for U.S. federal income tax purposes.

Tax Cuts and Jobs Act

Under tax legislation signed into law in December 2017 commonly known as the Tax Cuts and Jobs Act of 2017, U.S. Holders that use an accrual method of accounting for tax purposes and have certain financial statements generally will be required to include certain amounts in income no later than the time such amounts are taken into account as revenue in such financial statements. The application of this rule thus may require the accrual of income earlier than would be the case under the general tax rules described below, although the precise application of this rule is unclear at this time. U.S. Holders that use an accrual method of accounting should consult with their tax advisors regarding the potential applicability of this legislation to their particular situation.

Allocation of Purchase Price Between our Common Stock and Warrants

For U.S. federal income tax purposes, the common stock and Warrants issued pursuant to this offering will be treated as an "investment unit" consisting of one share of common stock and the accompanying Warrants to acquire our common stock. The purchase price for each investment unit will be allocated between these two components in proportion to their relative fair market values at the time the unit is purchased by the holder. This allocation of the purchase price for each unit will establish the holder's initial tax basis for U.S. federal income tax purposes in the share of common stock and the Warrants included in each unit. The separation of the share of common stock and the Warrants included in each unit should not be a taxable event for U.S. federal income tax purposes. Each holder should consult his, her or its own tax advisor regarding the allocation of the purchase price between the common stock and the Warrants.

Election not to Accept Warrants

This discussion does not address the federal income tax consequences to an opt-out investor of electing not to accept Warrants. Each holder should consult his, her or its own tax advisor regarding the federal income tax consequences of electing not to accept Warrants, including the impact on the holder's tax basis in its common stock and Warrants, if any.

Tax Considerations Applicable to U.S. Holders

Exercise and Expiration of Warrants

In general, a U.S. Holder will not recognize gain or loss for U.S. federal income tax purposes upon exercise of a Warrant. The U.S. Holder will take a tax basis in the shares acquired on the exercise of a

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Warrant equal to the exercise price of the Warrant, increased by the U.S. Holder's adjusted tax basis in the Warrant exercised (as determined pursuant to the rules discussed above). The U.S. Holder's holding period in the shares of our common stock acquired on exercise of the Warrant will begin on the date of exercise of the Warrant or possibly the day after such exercise, and will not include any period for which the U.S. Holder held the Warrant.

The lapse or expiration of a Warrant will be treated as if the U.S. Holder sold or exchanged the Warrant and recognized a capital loss equal to the U.S. Holder's tax basis in the Warrant. The deductibility of capital losses is subject to limitations.

Distributions

As discussed above, we currently anticipate that we will retain future earnings, if any, to finance the growth and development of our business and do not intend to pay cash dividends in respect of our common stock in the foreseeable future. In the event that we do make distributions on our common stock to a U.S. Holder, those distributions generally will constitute dividends for U.S. tax purposes to the extent paid out of our current or accumulated earnings and profits (as determined under U.S. federal income tax principles). Distributions in excess of our current and accumulated earnings and profits will constitute a return of capital that is applied against and reduces, but not below zero, a U.S. Holder's adjusted tax basis in our common stock. Any remaining excess will be treated as gain realized on the sale or exchange of our common stock as described below under the section titled "—Disposition of Our Common Stock or Warrants."

Certain Adjustments to Warrants

The number of shares of common stock issued on the exercise of the Warrants and the exercise price of Warrants are subject to adjustment in certain circumstances. Adjustments (or failure to make adjustments) that have the effect of increasing a U.S. Holder's proportionate interest in our assets or earnings and profits may, in some circumstances, result in a constructive distribution to the U.S. Holder. Adjustments to the conversion rate made pursuant to a bona fide reasonable adjustment formula which has the effect of preventing the dilution of the interest of the holders of Warrants generally will not be deemed to result in a constructive distribution. If an adjustment is made that does not qualify as being made pursuant to a bona fide reasonable adjustment formula, a U.S. Holder of Warrants may be deemed to have received a constructive distribution from us, even though such U.S. Holder has not received any cash or property as a result of such adjustment. The tax consequences of the receipt of a distribution from us are described above under "Distributions."

Disposition of Our Common Stock or Warrants

Upon a sale or other taxable disposition (other than a redemption treated as a distribution, which will be taxed as described above under "Distributions") of our common stock or Warrants, a U.S. Holder generally will recognize capital gain or loss in an amount equal to the difference between the amount realized and the U.S. Holder's adjusted tax basis in the common stock or Warrants. Capital gain or loss will constitute long-term capital gain or loss if the U.S. Holder's holding period for the common stock or Warrants exceeds one year. The deductibility of capital losses is subject to certain limitations. U.S. Holders who recognize losses with respect to a disposition of our common stock or Warrants should consult their own tax advisors regarding the tax treatment of such losses.

Information Reporting and Backup Reporting

Information reporting requirements generally will apply to payments of dividends (including constructive dividends) on the common stock and Warrants and to the proceeds of a sale or other disposition of common stock and Warrants paid by us to a U.S. Holder unless such U.S. Holder is an exempt recipient, such as a corporation. Backup withholding will apply to those payments if the U.S.

Holder fails to provide the holder's taxpayer identification number, or certification of exempt status, or if the holder otherwise fails to comply with applicable requirements to establish an exemption.

Backup withholding is not an additional tax. Rather, any amounts withheld under the backup withholding rules will be allowed as a refund or a credit against the U.S. Holder's U.S. federal income tax liability provided the required information is timely furnished to the IRS. U.S. Holders should consult their own tax advisors regarding their qualification for exemption from information reporting and backup withholding and the procedure for obtaining such exemption.

Tax Considerations Applicable to Non-U.S. Holders

Exercise and Expiration of Warrants

In general, a Non-U.S. Holder will not recognize gain or loss for U.S. federal income tax purposes upon the exercise of Warrants into shares of common stock.

The expiration of a Warrant will be treated as if the Non-U.S. Holder sold or exchanged the Warrant and recognized a capital loss equal to the Non-U.S. Holder's tax basis in the Warrant. However, a Non-U.S. Holder will not be able to utilize a loss recognized upon expiration of a Warrant against the Non-U.S. Holder's U.S. federal income tax liability unless the loss is effectively connected with the Non-U.S. Holder's conduct of a trade or business within the United States (and, if an income tax treaty applies, is attributable to a permanent establishment or fixed base in the United States) or is treated as a U.S.-source loss and the Non-U.S. Holder is present 183 days or more in the taxable year of disposition and certain other conditions are met.

Certain Adjustments to Warrants

As described under "—U.S. Holders—Certain Adjustments to Warrants," an adjustment to the Warrants could result in a constructive distribution to a Non-U.S. Holder, which would be treated as described under "Distributions" below. Any resulting withholding tax attributable to deemed dividends would be collected from other amounts payable or distributable to the Non-U.S. Holder. Non-U.S. Holders should consult their tax advisors regarding the proper treatment of any adjustments to the Warrants.

Distributions

As discussed above, we currently anticipate that we will retain future earnings, if any, to finance the growth and development of our business and do not intend to pay cash dividends in respect of our common stock in the foreseeable future. In the event that we do make distributions on our common stock to a Non-U.S. Holder, those distributions generally will constitute dividends for U.S. federal income tax purposes as described in "—U.S. Holders—Distributions."

Any distribution (including constructive distributions) on our common stock that is treated as a dividend paid to a Non-U.S. Holder that is not effectively connected with the holder's conduct of a trade or business in the United States will generally be subject to withholding tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and the Non-U.S. Holder's country of residence. To obtain a reduced rate of withholding under a treaty, a Non-U.S. Holder generally will be required to provide the applicable withholding agent with a properly executed IRS Form W-8BEN, IRS Form W-8BEN-E or other appropriate form, certifying the Non-U.S. Holder's entitlement to benefits under that treaty. Such form must be provided prior to the payment of dividends and must be updated periodically. If a Non-U.S. Holder holds stock through a financial institution or other agent acting on the holder's behalf, the holder will be required to provide appropriate documentation to such agent. The holder's agent may then be required to provide certification to the applicable withholding agent, either directly or through other intermediaries. If you are eligible for a reduced rate of U.S. withholding tax under an income tax treaty, you should consult with your own tax

advisor to determine if you are able to obtain a refund or credit of any excess amounts withheld by timely filing an appropriate claim for a refund with the IRS.

We generally are not required to withhold tax on dividends paid (or constructive dividends deemed paid) to a Non-U.S. Holder that are effectively connected with the holder's conduct of a trade or business within the United States (and, if required by an applicable income tax treaty, are attributable to a permanent establishment or fixed base that the holder maintains in the United States) if a properly executed IRS Form W-8ECI, stating that the dividends are so connected, is furnished to us (or, if stock is held through a financial institution or other agent, to the applicable withholding agent). In general, such effectively connected dividends will be subject to U.S. federal income tax on a net income basis at the regular tax rates applicable to U.S. persons. A corporate Non-U.S. Holder receiving effectively connected dividends may also be subject to an additional "branch profits tax," which is imposed, under certain circumstances, at a rate of 30% (or such lower rate as may be specified by an applicable treaty) on the corporate Non-U.S. Holder's effectively connected earnings and profits, subject to certain adjustments.

See also the sections below titled "—Backup Withholding and Information Reporting" and "—Foreign Accounts" for additional withholding rules that may apply to dividends paid to certain foreign financial institutions or non-financial foreign entities.

Disposition of Our Common Stock or Warrants

Subject to the discussions below under the sections titled "—Backup Withholding and Information Reporting" and "—Foreign Accounts," a Non-U.S. Holder generally will not be subject to U.S. federal income or withholding tax with respect to gain recognized on a sale or other disposition (other than a redemption treated as a distribution, which will be taxable as described above under "Distributions") of our common stock or Warrants unless:

- the gain is effectively connected with the Non-U.S. Holder's conduct of a trade or business in the United States, and if an applicable income tax treaty so provides, the gain is attributable to a permanent establishment or fixed base maintained by the Non-U.S. Holder in the United States; in these cases, the Non-U.S. Holder will be taxed on a net income basis at the regular tax rates and in the manner applicable to U.S. persons, and if the Non-U.S. Holder is a corporation, an additional branch profits tax at a rate of 30%, or a lower rate as may be specified by an applicable income tax treaty, may also apply;
- the Non-U.S. Holder is a nonresident alien present in the United States for 183 days or more in the taxable year of the disposition and certain other requirements are met, in which case the Non-U.S. Holder will be subject to a 30% tax (or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder's country of residence) on the net gain derived from the disposition, which may be offset by certain U.S.-source capital losses of the Non-U.S. Holder, if any; or
- our common stock constitutes a U.S. real property interest because we are, or have been at any time during the five-year period preceding such disposition (or the Non-U.S. Holder's holding period of the common stock or Warrants, if shorter), a "U.S. real property holding corporation," unless our common stock is regularly traded on an established securities market and the Non-U.S. Holder held no more than 5% of our outstanding common stock, directly or indirectly, during the shorter of the five-year period ending on the date of the disposition or the period that the Non-U.S. Holder held our common stock. Special rules may apply to the determination of the 5% threshold in the case of a holder of Warrants. Non-U.S. Holders are urged to consult their own tax advisors regarding the effect of holding our Warrants on the calculation of such 5% threshold. Generally, a corporation is a "U.S. real property holding corporation" if the fair market value of its "U.S. real property interests" (as defined in the Code and applicable regulations) equals or exceeds 50% of the sum of the fair market value of its

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worldwide real property interests plus its other assets used or held for use in a trade or business. Although there can be no assurance, we believe that we are not currently, and we do not anticipate becoming, a “U.S. real property holding corporation” for U.S. federal income tax purposes. No assurance can be provided that our common stock will be regularly traded on an established securities market for purposes of the rules described above. Non-U.S. Holders are urged to consult their own tax advisors regarding the U.S. federal income tax considerations that could result if we are, or become, a “U.S. real property holding corporation.”

See the sections titled “—Backup Withholding and Information Reporting” and “—Foreign Accounts” for additional information regarding withholding rules that may apply to proceeds of a disposition of our common stock or Warrants paid to foreign financial institutions or non-financial foreign entities.

Backup Withholding and Information Reporting

We must report annually to the IRS and to each Non-U.S. Holder the gross amount of the distributions (including constructive distributions) on our common stock or Warrants paid to such holder and the tax withheld, if any, with respect to such distributions. Non-U.S. Holders may have to comply with specific certification procedures to establish that the holder is not a U.S. person (as defined in the Code) in order to avoid backup withholding at the applicable rate, currently 24%, with respect to dividends (or constructive dividends) on our common stock or Warrants. Generally, a holder will comply with such procedures if it provides a properly executed IRS Form W-8BEN (or other applicable Form W-8) or otherwise meets documentary evidence requirements for establishing that it is a Non-U.S. Holder, or otherwise establishes an exemption. Dividends paid to Non-U.S. Holders subject to withholding of U.S. federal income tax, as described above under the heading “Dividends,” will generally be exempt from U.S. backup withholding.

Information reporting and backup withholding generally will apply to the proceeds of a disposition of our common stock or Warrants by a Non-U.S. Holder effected by or through the U.S. office of any broker, U.S. or foreign, unless the holder certifies its status as a Non-U.S. Holder and satisfies certain other requirements, or otherwise establishes an exemption. Generally, information reporting and backup withholding will not apply to a payment of disposition proceeds to a Non-U.S. Holder where the transaction is effected outside the United States through a non-U.S. office of a broker. However, for information reporting purposes, dispositions effected through a non-U.S. office of a broker with substantial U.S. ownership or operations generally will be treated in a manner similar to dispositions effected through a U.S. office of a broker. Non-U.S. Holders should consult their own tax advisors regarding the application of the information reporting and backup withholding rules to them.

Copies of information returns may be made available to the tax authorities of the country in which the Non-U.S. Holder resides or is incorporated under the provisions of a specific treaty or agreement.

Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules from a payment to a Non-U.S. Holder can be refunded or credited against the Non-U.S. Holder’s U.S. federal income tax liability, if any, provided that an appropriate claim is timely filed with the IRS.

Foreign Accounts

The Foreign Account Tax Compliance Act, or FATCA, generally imposes a 30% withholding tax on dividends (including constructive dividends) on, and gross proceeds from the sale or other disposition of, our common stock and Warrants if paid to a non-U.S. entity unless (i) if the non-U.S. entity is a “foreign financial institution,” the non-U.S. entity undertakes certain due diligence, reporting, withholding, and certification obligations, (ii) if the non-U.S. entity is not a “foreign financial institution,”

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the non-U.S. entity identifies certain of its U.S. investors, if any, or (iii) the non-U.S. entity is otherwise exempt under FATCA.

Withholding under FATCA generally will apply to payments of dividends (including constructive dividends) on our common stock and Warrants. While withholding under FATCA may apply to payments of gross proceeds from a sale or other disposition of our common stock or Warrants, under recently proposed U.S. Treasury Regulations withholding on payments of gross proceeds is not required. Although such regulations are not final, applicable withholding agents may rely on the proposed regulations until final regulations are issued.

An intergovernmental agreement between the United States and an applicable foreign country may modify the requirements described in this section. Under certain circumstances, a holder may be eligible for refunds or credits of the tax. Holders should consult their own tax advisors regarding the possible implications of FATCA on their investment in our common stock or Warrants.

Federal Estate Tax

Common stock owned or treated as owned by an individual who is not a citizen or resident of the United States (as specially defined for U.S. federal estate tax purposes) at the time of death will be included in the individual's gross estate for U.S. federal estate tax purposes and, therefore, may be subject to U.S. federal estate tax, unless an applicable estate tax or other treaty provides otherwise. The foregoing may also apply to Warrants. A Non-U.S. Holder should consult his, her, or its own tax advisor regarding the U.S. federal estate tax consequences of the ownership or disposition of shares of our common stock and Warrants.

The preceding discussion of material U.S. federal tax considerations is for information only. It is not tax advice. Prospective investors should consult their own tax advisors regarding the particular U.S. federal, state, local and non-U.S. tax consequences of purchasing, holding and disposing of our common stock or Warrants, including the consequences of any proposed changes in applicable laws.

UNDERWRITING

We and the underwriters for the offering named below have entered into an underwriting agreement with respect to the securities being offered. Subject to the terms and conditions of the underwriting agreement, each underwriter has severally agreed to purchase from us the number of shares of our common stock and Warrants set forth opposite its name below. Cowen and Company, LLC and Piper Jaffray & Co. are the representatives of the underwriters.

<u>Underwriter</u>	<u>Number of Shares</u>	<u>Number of Warrants</u>
Cowen and Company, LLC	3,553,607	800,256
Piper Jaffray & Co.	3,120,240	702,664
JMP Securities LLC	1,300,100	292,777
Roth Capital Partners, LLC	693,386	156,147
Total	8,667,333	1,951,844

The underwriting agreement provides that the obligations of the underwriters are subject to certain conditions precedent and that the underwriters have agreed, severally and not jointly, to purchase all of the number of shares of common stock and Warrants sold under the underwriting agreement if any of these shares and Warrants are purchased. If an underwriter defaults, the underwriting agreement provides that the purchase commitments of the non-defaulting underwriters may be increased or the offering may be terminated.

We have agreed to indemnify the underwriters against specified liabilities, including liabilities under the Securities Act of 1933, as amended, or the Securities Act, and to contribute to payments the underwriters may be required to make in respect thereof.

Our common stock is listed on the Nasdaq Global Select Market under the symbol "SYRS." There is no established public trading market for the Warrants, and we do not expect a market to develop. We do not intend to list the Warrants on the Nasdaq Global Select Market, any other national securities exchange or any other nationally recognized trading system.

The underwriters are offering the shares and the accompanying Warrants, subject to prior sale, when, as and if issued to and accepted by them, subject to approval of legal matters by their counsel and other conditions specified in the underwriting agreement. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part.

Discounts and Commissions. The following table shows the public offering price, underwriting discounts and commissions and proceeds, before expenses, to us.

	<u>Per Share and Accompanying Warrants</u>	<u>Total</u>
Public offering price	\$ 7.50	\$65,004,998
Underwriting discounts and commissions	\$ 0.45	\$ 3,900,300
Proceeds, before expenses, to Syros	\$ 7.05	\$61,104,698

We estimate that the total expenses of this offering and the Concurrent Offering, excluding underwriting discounts and commissions, will be approximately \$400,000 and are payable by us. We have agreed to reimburse the underwriters for expenses of up to \$30,000 related to clearance of this offering and the Concurrent Offering with the Financial Industry Regulatory Authority, Inc., or FINRA.

The underwriters propose to offer the shares of common stock and the accompanying Warrants to the public at the public offering price set forth on the cover of this prospectus. The underwriters may offer these securities to securities dealers at the public offering price less a concession not in excess of

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\$0.27 per share and accompanying Warrants. If all of the securities are not sold at the public offering price, the underwriters may change the offering price and other selling terms. Sales of securities made outside of the United States may be made by affiliates of certain of the underwriters. Certain of the underwriters may sell securities to the public through one or more of their affiliates as selling agents.

Discretionary Accounts. The underwriters do not intend to confirm sales of the securities to any accounts over which they have discretionary authority.

Passive Market Making. In connection with this offering, underwriters and selling group members may engage in passive market making transactions in our common stock on the Nasdaq Stock Market in accordance with Rule 103 of Regulation M under the Securities Exchange Act of 1934, as amended, or the Exchange Act, during a period before the commencement of offers or sales of common stock and extending through the completion of the distribution. A passive market maker must display its bid at a price not in excess of the highest independent bid of that security. However, if all independent bids are lowered below the passive market maker's bid, such bid must then be lowered when specified purchase limits are exceeded.

Lock-Up Agreements. Pursuant to certain "lock-up" agreements, we and our executive officers and directors and certain of our stockholders, have agreed, subject to certain exceptions, not to offer, sell, assign, transfer, pledge, contract to sell, or otherwise dispose of or announce the intention to otherwise dispose of, or enter into any swap, hedge or similar agreement or arrangement that transfers, in whole or in part, the economic risk of ownership of, directly or indirectly, or make any demand or request or exercise any right with respect to the registration of, any common stock or securities convertible into or exchangeable or exercisable for any common stock without the prior written consent of Cowen and Company, LLC and Piper Jaffray & Co., for a period of 60 days after the date of this prospectus supplement.

This lock-up provision applies to common stock and to securities convertible into or exchangeable or exercisable for common stock. It also applies to common stock owned now or acquired later by the person executing the agreement or for which the person executing the agreement later acquires the power of disposition. The lock-up agreements include customary exceptions.

Cowen and Company, LLC and Piper Jaffray & Co., in their sole discretion, may release our common stock and other securities subject to the lock-up agreements described above in whole or in part at any time. When determining whether or not to release our common stock and other securities from lock-up agreements, Cowen and Company, LLC and Piper Jaffray & Co. will consider, among other factors, the holder's reasons for requesting the release, the number of shares for which the release is being requested and market conditions at the time of the request.

Canada. Our securities may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 *Prospectus Exemptions* or subsection 73.3(1) of the *Securities Act* (Ontario), and are permitted clients, as defined in National Instrument 31-103 *Registration Requirements, Exemptions and Ongoing Registrant Obligations*. Any resale of our securities must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus supplement (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

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Pursuant to section 3A.3 of National Instrument 33-105 *Underwriting Conflicts* (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

United Kingdom. Each of the underwriters has represented and agreed that:

- it has not made or will not make an offer of the securities to the public in the United Kingdom within the meaning of section 102B of the Financial Services and Markets Act 2000 (as amended), or the FSMA, except to legal entities which are authorized or regulated to operate in the financial markets or, if not so authorized or regulated, whose corporate purpose is solely to invest in securities or otherwise in circumstances which do not require the publication by us of a prospectus pursuant to the Prospectus Rules of the Financial Services Authority, or FSA;
- it has only communicated or caused to be communicated and will only communicate or cause to be communicated an invitation or inducement to engage in investment activity (within the meaning of section 21 of FSMA) to persons who have professional experience in matters relating to investments falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 or in circumstances in which section 21 of FSMA does not apply to us; and
- it has complied with and will comply with all applicable provisions of FSMA with respect to anything done by it in relation to the securities in, from or otherwise involving the United Kingdom.

Switzerland. The securities will not be offered, directly or indirectly, to the public in Switzerland and this prospectus supplement does not constitute a public offering prospectus as that term is understood pursuant to article 652a or 1156 of the Swiss Federal Code of Obligations.

Israel. In the State of Israel this prospectus supplement shall not be regarded as an offer to the public to purchase securities under the Israeli Securities Law, 5728—1968, which requires a prospectus to be published and authorized by the Israel Securities Authority, if it complies with certain provisions of Section 15 of the Israeli Securities Law, 5728—1968, including, *inter alia*, if: (i) the offer is made, distributed or directed to not more than 35 investors, subject to certain conditions (the “Addressed Investors”); or (ii) the offer is made, distributed or directed to certain qualified investors defined in the First Addendum of the Israeli Securities Law, 5728—1968, subject to certain conditions (the “Qualified Investors”). The Qualified Investors shall not be taken into account in the count of the Addressed Investors and may be offered to purchase securities in addition to the 35 Addressed Investors. The company has not and will not take any action that would require it to publish a prospectus in accordance with and subject to the Israeli Securities Law, 5728—1968. We have not and will not distribute this prospectus supplement or make, distribute or direct an offer to subscribe for our securities to any person within the State of Israel, other than to Qualified Investors and up to 35 Addressed Investors.

Qualified Investors may have to submit written evidence that they meet the definitions set out in of the First Addendum to the Israeli Securities Law, 5728—1968. In particular, we may request, as a condition to be offered securities, that Qualified Investors will each represent, warrant and certify to us and/or to anyone acting on our behalf: (i) that it is an investor falling within one of the categories listed in the First Addendum to the Israeli Securities Law, 5728—1968; (ii) which of the categories listed in the First Addendum to the Israeli Securities Law, 5728—1968 regarding Qualified Investors is applicable to it; (iii) that it will abide by all provisions set forth in the Israeli Securities Law, 5728—1968 and the regulations promulgated thereunder in connection with the offer to be issued securities; (iv) that the securities that it will be issued are, subject to exemptions available under the Israeli Securities Law, 5728—1968: (a) for its own account; (b) for investment purposes only; and (c) not issued with a view to resale within the State of Israel, other than in accordance with the provisions of

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the Israeli Securities Law, 5728—1968; and (v) that it is willing to provide further evidence of its Qualified Investor status. Addressed Investors may have to submit written evidence in respect of their identity and may have to sign and submit a declaration containing, *inter alia*, the Addressed Investor's name, address and passport number or Israeli identification number.

European Economic Area. In relation to each Member State of the European Economic Area, or the EEA, which has implemented the European Prospectus Directive (each, a "Relevant Member State"), an offer of our securities may not be made to the public in a Relevant Member State other than:

- to any legal entity which is a qualified investor, as defined in the European Prospectus Directive;
- to fewer than 150 natural or legal persons (other than qualified investors as defined in the European Prospectus Directive), subject to obtaining the prior consent of the relevant dealer or dealers nominated by us for any such offer; or
- in any other circumstances falling within Article 3(2) of the European Prospectus Directive;

provided that no such offer of our securities shall require us or any underwriter to publish a prospectus pursuant to Article 3 of the European Prospectus Directive or supplement prospectus pursuant to Article 16 of the European Prospectus Directive and each person who initially acquires any securities or to whom any offer is made will be deemed to have represented, acknowledged and agreed to and with each of the underwriters and with us that it is a "qualified investor" within the meaning of the law in that Relevant Member State implementing Article 2(1) (e) of the European Prospectus Directive.

In the case of any securities being offered to a financial intermediary as that term is used in Article 3(2) of the European Prospectus Directive, each such financial intermediary will be deemed to have represented, acknowledged and agreed that the securities acquired by it in the offer have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in circumstances which may give rise to an offer or any securities to the public other than their offer or resale in a Relevant Member State to qualified investors as so defined or in circumstances in which the prior consent of the representatives has been obtained to each such proposed offer or resale.

For the purposes of this description, the expression an "offer to the public" in relation to the securities in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the securities to be offered so as to enable an investor to decide to purchase or subscribe for the securities, as the expression may be varied in that Relevant Member State by any measure implementing the European Prospectus Directive in that member state, and the expression "European Prospectus Directive" means Directive 2003/71/EC (and amendments hereto, including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member State) and includes any relevant implementing measure in each Relevant Member State. The expression 2010 PD Amending Directive means Directive 2010/73/EU.

Hong Kong. The contents of this document have not been reviewed or approved by any regulatory authority in Hong Kong. This document does not constitute an offer or invitation to the public in Hong Kong to acquire our securities. Accordingly, unless permitted by the securities laws of Hong Kong, no person may issue or have in its possession for the purposes of issue, this document or any advertisement, invitation or document relating to the securities, whether in Hong Kong or elsewhere, which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong other than in relation to securities which are intended to be disposed of only to persons outside Hong Kong or only to "professional investors" (as such term is defined in the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) ("SFO") and the subsidiary legislation made thereunder); or in circumstances which do not result in this document being a "prospectus" as defined in the

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Companies (Winding Up and Miscellaneous Provisions) Ordinance (Cap. 32, Laws of Hong Kong) (“CO”); or which do not constitute an offer or an invitation to the public for the purposes of the SFO or the CO. The offer of the securities is personal to the person to whom this document has been delivered, and a subscription for securities will only be accepted from such person. No person to whom a copy of this document is issued may issue, circulate or distribute this document in Hong Kong, or make or give a copy of this document to any other person. You are advised to exercise caution in relation to the offer. If you are in any doubt about any of the contents of this document, you should obtain independent professional advice.

Singapore. This prospectus supplement has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus supplement and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the securities may not be circulated or distributed, nor may the securities be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor pursuant to Section 274 of the Securities and Futures Act, Chapter 289 of Singapore (“SFA”), (ii) to a relevant person (as defined in Section 275(2) of the SFA), or any person pursuant to Section 275(1A), and in accordance with the conditions, specified in Section 275 of the SFA, or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

Where the securities are subscribed or purchased pursuant to an offer made in reliance on Section 275 of the SFA by a relevant person which is:

- (a) a corporation (which is not an accredited investor) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or
- (b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary is an accredited investor;

shares, debentures and units of shares, and debentures of that corporation, or the beneficiaries’ rights and interest (howsoever described) in that trust shall not be transferable for six months after that corporation or that trust has acquired the securities under Section 275 except:

- (1) to an institutional investor or to a relevant person (as defined in Section 275(2) of the SFA), or any person pursuant to Section 275(1A) of the SFA (in the case of that corporation) or Section 276(4)(i)(B) of the SFA (in the case of that trust);
- (2) where no consideration is or will be given for the transfer; or
- (3) where the transfer is by operation of law.

Electronic Offer, Sale and Distribution of Shares. A prospectus in electronic format may be made available on the websites maintained by one or more of the underwriters or selling group members, if any, participating in this offering and one or more of the underwriters participating in this offering may distribute prospectuses electronically. The representatives may agree to allocate a number of shares and accompanying Warrants to underwriters and selling group members for sale to their online brokerage account holders. Internet distributions will be allocated by the underwriters and selling group members that will make internet distributions on the same basis as other allocations. Other than the prospectus in electronic format, the information on these websites is not part of this prospectus or the registration statement of which this prospectus forms a part, has not been approved or endorsed by us or any underwriter in its capacity as underwriter, and should not be relied upon by investors.

Other Relationships. Certain of the underwriters and their affiliates have provided, and may in the future provide, various investment banking, commercial banking and other financial services for us and our affiliates for which they have received, and may in the future receive, customary fees.

LEGAL MATTERS

The validity of the securities offered hereby will be passed upon for us by Wilmer Cutler Pickering Hale and Dorr LLP, Boston, Massachusetts. Cooley LLP, Boston, Massachusetts, has acted as counsel for the underwriters in connection with certain legal matters related to this offering.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2018, as set forth in their report, which is incorporated by reference in this prospectus supplement and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We file reports, proxy statements and other documents with the SEC. Our SEC filings are available to you on the SEC's Internet site at www.sec.gov.

This prospectus supplement is part of a registration statement that we filed with the SEC. The registration statement contains more information than this prospectus supplement regarding us and our securities, including certain exhibits and schedules. You can obtain a copy of the registration statement from the SEC at the address listed above or from the SEC's Internet site.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC requires us to "incorporate" into this prospectus supplement information that we file with the SEC in other documents. This means that we can disclose important information to you by referring to other documents that contain that information. The information incorporated by reference is considered to be part of this prospectus supplement and the accompanying prospectus. Information contained in this prospectus supplement and the accompanying prospectus and information that we file with the SEC in the future and incorporate by reference in this prospectus supplement automatically updates and supersedes previously filed information. We incorporate by reference the documents listed below and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus supplement and prior to the sale of all the securities covered by this prospectus supplement.

- Our Annual Report on Form 10-K for the year ended December 31, 2018, filed with the SEC on March 7, 2019;
- The information specifically incorporated by reference into the Annual Report on Form 10-K for the year ended December 31, 2017 from our definitive proxy statement for the 2018 Annual Meeting of Stockholders filed on April 26, 2018;
- Our Current Reports on Form 8-K filed with the SEC on January 7, 2019 (except Item 7.01) and January 11, 2019; and
- The description of our common stock contained in our Registration Statement on Form 8-A/A filed on July 20, 2017, including any amendments or reports filed for the purpose of updating such description.

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A statement contained in a document incorporated by reference into this prospectus supplement shall be deemed to be modified or superseded for purposes of this prospectus supplement to the extent that a statement contained in this prospectus supplement, the accompanying prospectus or in any other subsequently filed document which is also incorporated in this prospectus supplement modifies or replaces such statement. Any statements so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus supplement.

You may request a copy of these documents, which will be provided to you at no cost, by writing or telephoning us using the following contact information:

Syros Pharmaceuticals, Inc.
620 Memorial Drive, Suite 300
Cambridge, Massachusetts, 02139
Attention: Gerald E. Quirk, Chief Legal and Administrative Officer & Secretary
Telephone: (617) 744-1340

PROSPECTUS

SYROS PHARMACEUTICALS, INC.



**\$225,000,000
of
Debt Securities
Common Stock
Preferred Stock
Units
Warrants**

We may offer and sell securities from time to time in one or more offerings of up to \$225,000,000 in aggregate offering price. This prospectus describes the general terms of these securities and the general manner in which these securities will be offered. We will provide the specific terms of these securities in supplements to this prospectus. The prospectus supplements will also describe the specific manner in which these securities will be offered and may also supplement, update or amend information contained in this document. You should read this prospectus and any applicable prospectus supplement before you invest.

We may offer these securities in amounts, at prices and on terms determined at the time of offering. The securities may be sold directly to you, through agents, or through underwriters and dealers. If agents, underwriters or dealers are used to sell the securities, we will name them and describe their compensation in a prospectus supplement.

Our common stock is listed on The NASDAQ Global Select Market under the symbol "SYRS."

Investing in these securities involves certain risks. See "[Risk Factors](#)" on page 7 of this prospectus and in any accompanying prospectus supplement and in the documents incorporated by reference in this prospectus for a discussion of the factors you should carefully consider before deciding to purchase these securities.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

The date of this prospectus is July 31, 2017

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, which we refer to as the “SEC,” utilizing a “shelf” registration process. Under this shelf registration process, we may from time to time sell any combination of the securities described in this prospectus in one or more offerings for an aggregate initial offering price of up to \$225,000,000.

This prospectus provides you with a general description of the securities we may offer. Each time we sell securities, we will provide one or more prospectus supplements that will contain specific information about the terms of the offering. The prospectus supplement may also add, update or change information contained in this prospectus. You should read both this prospectus and the accompanying prospectus supplement together with the additional information described under the heading “Where You Can Find More Information” beginning on page 2 of this prospectus.

You should rely only on the information contained in or incorporated by reference in this prospectus, in any accompanying prospectus supplement or in any related free writing prospectus filed by us with the SEC. We have not authorized anyone to provide you with different information. This prospectus and any accompanying prospectus supplement do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the securities described in this prospectus or such accompanying prospectus supplement or an offer to sell or the solicitation of an offer to buy such securities in any circumstances in which such offer or solicitation is unlawful. You should assume that the information appearing in this prospectus, any prospectus supplement, the documents incorporated by reference and any related free writing prospectus is accurate only as of their respective dates. Our business, financial condition, results of operations and prospects may have changed materially since those dates.

Unless the context otherwise indicates, references in this prospectus to “we,” “our” and “us” refer, collectively, to Syros Pharmaceuticals, Inc., a Delaware corporation, and its consolidated subsidiary.

The Syros logo, “Syros” and “Syros Pharmaceuticals” are our trademarks. Solely for convenience, the trademarks and trade names in this prospectus are referred to without the ® and ™ symbols, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto. The trademarks, trade names and service marks appearing in this prospectus are the property of their respective owners.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at <http://www.sec.gov>. Copies of certain information filed by us with the SEC are also available on our website at www.syros.com. Our website is not a part of this prospectus and is not incorporated by reference in this prospectus. You may also read and copy any document we file at the SEC's Public Reference Room, 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information on the operation of the Public Reference Room.

This prospectus is part of a registration statement we filed with the SEC. This prospectus omits some information contained in the registration statement in accordance with SEC rules and regulations. You should review the information and exhibits in the registration statement for further information about us and our consolidated subsidiary and the securities we are offering. Statements in this prospectus concerning any document we filed as an exhibit to the registration statement or that we otherwise filed with the SEC are not intended to be comprehensive and are qualified by reference to these filings. You should review the complete document to evaluate these statements.

INCORPORATION BY REFERENCE

The SEC allows us to incorporate by reference much of the information we file with the SEC, which means that we can disclose important information to you by referring you to those publicly available documents. The information that we incorporate by reference in this prospectus is considered to be part of this prospectus. Because we are incorporating by reference future filings with the SEC, this prospectus is continually updated and those future filings may modify or supersede some of the information included or incorporated in this prospectus. This means that you must look at all of the SEC filings that we incorporate by reference to determine if any of the statements in this prospectus or in any document previously incorporated by reference have been modified or superseded. This prospectus incorporates by reference the documents listed below (File No. 001-37813) and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act (in each case, other than those documents or the portions of those documents not deemed to be filed) between the date of the initial registration statement and the effectiveness of the registration statement and following the effectiveness of the registration statement, until the offering of the securities under the registration statement is terminated or completed:

- Annual Report on Form 10-K for the fiscal year ended December 31, 2016, including the information specifically incorporated by reference into the Annual Report on Form 10-K from our definitive proxy statement for the 2017 Annual Meeting of Stockholders;
- Quarterly Report on Form 10-Q for the fiscal quarter ended March 31, 2017;
- Current Reports on Form 8-K filed January 9, 2017, January 30, 2017, April 21, 2017, April 26, 2017 and June 12, 2017; and
- The description of our common stock contained in our Registration Statement on Form 8-A filed on June 27, 2016, including any amendments or reports filed for the purpose of updating such description.

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You may request a copy of these filings, at no cost, by writing or telephoning us at the following address or telephone number:

Syros Pharmaceuticals, Inc.
620 Memorial Drive, Suite 300
Cambridge, Massachusetts, 02139
Attention: Gerald E. Quirk, Chief Legal and Administrative Officer & Secretary
Telephone: (617) 744-1340

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the information incorporated by reference in this prospectus include “forward-looking statements” within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. All statements, other than statements of historical facts, contained in this prospectus or incorporated by reference herein, 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 prospectus and incorporated by reference herein are based upon information available to us as of the date such statements are made and, while we believe such information forms a reasonable basis for such statements at the time made, 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 clinical trials of our product candidates, including 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;
- the impact of government laws and regulations; and

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- other risks and uncertainties, including those listed under the caption “Risk Factors” in our most recent Annual Report on Form 10-K, our most recent Quarterly Report on Form 10-Q, and other filings we make with the SEC.

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 or incorporated by reference in this prospectus. We have included important factors in the cautionary statements included or incorporated by reference in this prospectus, 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 prospectus, the documents incorporated by reference in this prospectus and the documents that we have filed as exhibits to the registration statement of which this prospectus is a part 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 prospectus includes and incorporates by reference certain 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 or incorporated by reference in this prospectus 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 section titled “Risk Factors.” These and other factors could cause results to differ materially from those expressed in the estimates made by the independent parties and by us.

SYROS PHARMACEUTICALS, INC.

Overview

We are a biopharmaceutical company pioneering an understanding of the non-coding 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. We are currently focused on developing treatments for cancer and immune-mediated diseases and are building a pipeline of gene control medicines. Our lead drug candidates are SY-1425, a selective retinoic acid receptor alpha, or RAR α , agonist in a Phase 2 clinical trial in genomically defined subsets of patients with acute myeloid leukemia and myelodysplastic syndrome, and SY-1365, a selective inhibitor of cyclin-dependent kinase 7, or CDK7, in a Phase 1 clinical trial in patients with advanced solid tumors, including transcriptionally dependent cancers such as triple-negative breast, small cell lung and ovarian cancers. We also have multiple programs in earlier stages of research and development in oncology, including immuno-oncology, autoimmune disorders and genetic diseases. Our goal is to build a fully integrated biopharmaceutical company based on our leadership position in gene control.

Corporate Information

We were incorporated under the laws of the State of Delaware on November 9, 2011 under the name LS22, Inc. Our principal executive offices are located at 620 Memorial Drive, Suite 300, Cambridge, Massachusetts 02139, and our telephone number is (617) 744-1340. Our internet address is www.syros.com. The information on our web site is not incorporated by reference into this prospectus and should not be considered to be a part of this prospectus. Our internet address is included in this prospectus as an inactive textual reference only.

RISK FACTORS

Investing in our common stock involves a high degree of risk. Before you decide to invest in our common stock, you should carefully consider the risks described in the section captioned "Risk Factors" in our most recent Annual Report on Form 10-K, our most recent Quarterly Report on Form 10-Q and other filings we make with the SEC from time to time, which are incorporated by reference herein in their entirety, together with the other information in this prospectus and documents incorporated by reference in this prospectus. The risks described in our most recent Annual Report on Form 10-K, our most recent Quarterly Report on Form 10-Q and the other filings incorporated by reference herein are not the only ones facing our company. Additional risks and uncertainties may also impair our business operations. If any of the risks described in our most recent Annual Report on Form 10-K, our most recent Quarterly Report on Form 10-Q and the other filings incorporated by reference herein occurs, our business, financial condition, results of operations and future growth prospects could be harmed. In these circumstances, the market price of our common stock could decline, and you may lose all or part of your investment.

CONSOLIDATED RATIOS OF EARNINGS TO FIXED CHARGES AND RATIOS OF EARNINGS TO COMBINED FIXED CHARGES AND PREFERRED STOCK DIVIDENDS

The following table sets forth our ratio of earnings to fixed charges and the ratio of earnings to combined fixed charges and preferred stock dividends for each of the periods indicated. You should read this table in conjunction with the consolidated financial statements and notes incorporated by reference in this prospectus.

	Three Months Ended March 31, 2017	Fiscal Year Ended			
		December 31, 2016	December 31, 2015	December 31, 2014	December 31, 2013
Consolidated ratios of earnings to fixed charges	N/A	N/A	N/A	N/A	N/A
Consolidated ratios of earnings to combined fixed charges and preferred stock dividends	N/A	N/A	N/A	N/A	N/A

For purposes of calculating the ratios above, earnings consist of net loss. Fixed charges include interest expense related to indebtedness and the interest portion of rent expense which is deemed to be representative of the interest factor.

Our earnings were insufficient to cover fixed charges in such periods and we are unable to disclose a ratio of earnings to fixed charges for such periods. Due to our losses for the years ended December 31, 2016, 2015, 2014 and 2013, and the three-month period ended March 31, 2017, the ratio coverage was less than 1:1. We would have needed to generate additional earnings of \$47.7 million, \$29.8 million, \$13.4 million, \$8.7 million and \$11.5 million, respectively, to achieve a coverage ratio of 1:1 in those periods.

We did not have any preferred stock outstanding after the completion of our initial public offering in July 2016.

USE OF PROCEEDS

We intend to use the net proceeds from the sale of any securities offered under this prospectus for general corporate purposes unless otherwise indicated in the applicable prospectus supplement. General corporate purposes may include research and development expenditures, acquisitions or in-licenses of complementary companies, medicines or technologies, expenditures to build out our development and commercial capabilities, repayment and refinancing of debt, working capital and capital expenditures. We may temporarily invest such net proceeds in investment-grade, interest-bearing securities until they are used for their stated purpose. We have not determined the amount of net proceeds to be used specifically for such purposes. As a result, management will retain broad discretion over the allocation of net proceeds.

DESCRIPTION OF DEBT SECURITIES

We may offer debt securities which may be senior or subordinated. We refer to the senior debt securities and the subordinated debt securities collectively as debt securities. The following description summarizes the general terms and provisions of the debt securities. We will describe the specific terms of the debt securities and the extent, if any, to which the general provisions summarized below apply to any series of debt securities in the prospectus supplement relating to the series and any applicable free writing prospectus that we authorize to be delivered. When we refer to “the Company,” “we,” “our,” and “us” in this section, we mean Syros Pharmaceuticals, Inc., excluding, unless the context otherwise requires or as otherwise expressly stated, our subsidiary.

We may issue senior debt securities from time to time, in one or more series under a senior indenture to be entered into between us and a senior trustee to be named in a prospectus supplement, which we refer to as the senior trustee. We may issue subordinated debt securities from time to time, in one or more series under a subordinated indenture to be entered into between us and a subordinated trustee to be named in a prospectus supplement, which we refer to as the subordinated trustee. The forms of senior indenture and subordinated indenture are filed as exhibits to the registration statement of which this prospectus forms a part. Together, the senior indenture and the subordinated indenture are referred to as the indentures and, together, the senior trustee and the subordinated trustee are referred to as the trustees. This prospectus briefly outlines some of the provisions of the indentures. The following summary of the material provisions of the indentures is qualified in its entirety by the provisions of the indentures, including definitions of certain terms used in the indentures. Wherever we refer to particular sections or defined terms of the indentures, those sections or defined terms are incorporated by reference in this prospectus or the applicable prospectus supplement. You should review the indentures that are filed as exhibits to the registration statement of which this prospectus forms a part for additional information.

None of the indentures will limit the amount of debt securities that we may issue. The applicable indenture will provide that debt securities may be issued up to an aggregate principal amount authorized from time to time by us and may be payable in any currency or currency unit designated by us or in amounts determined by reference to an index.

General

The senior debt securities will constitute our unsecured and unsubordinated general obligations and will rank pari passu with our other unsecured and unsubordinated obligations. The subordinated debt securities will constitute our unsecured and subordinated general obligations and will be junior in right of payment to our senior indebtedness (including senior debt securities), as described under the heading “—Certain Terms of the Subordinated Debt Securities—Subordination.” The debt securities will be structurally subordinated to all existing and future indebtedness and other liabilities of our subsidiaries unless such subsidiaries expressly guarantee such debt securities.

The debt securities will be our unsecured obligations. Any secured debt or other secured obligations will be effectively senior to the debt securities to the extent of the value of the assets securing such debt or other obligations.

The applicable prospectus supplement and/or free writing prospectus will include any additional or different terms of the debt securities of any series being offered, including the following terms:

- the title and type of the debt securities;
- whether the debt securities will be senior or subordinated debt securities, and, with respect to debt securities issued under the subordinated indenture the terms on which they are subordinated;

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- the aggregate principal amount of the debt securities;
- the price or prices at which we will sell the debt securities;
- the maturity date or dates of the debt securities and the right, if any, to extend such date or dates;
- the rate or rates, if any, per year, at which the debt securities will bear interest, or the method of determining such rate or rates;
- the date or dates from which such interest will accrue, the interest payment dates on which such interest will be payable or the manner of determination of such interest payment dates and the related record dates;
- the right, if any, to extend the interest payment periods and the duration of that extension;
- the manner of paying principal and interest and the place or places where principal and interest will be payable;
- provisions for a sinking fund, purchase fund or other analogous fund, if any;
- any redemption dates, prices, obligations and restrictions on the debt securities;
- the currency, currencies or currency units in which the debt securities will be denominated and the currency, currencies or currency units in which principal and interest, if any, on the debt securities may be payable;
- any conversion or exchange features of the debt securities;
- whether and upon what terms the debt securities may be defeased;
- any events of default or covenants in addition to or in lieu of those set forth in the indenture;
- whether the debt securities will be issued in definitive or global form or in definitive form only upon satisfaction of certain conditions;
- whether the debt securities will be guaranteed as to payment or performance;
- any special tax implications of the debt securities; and
- any other material terms of the debt securities.

When we refer to "principal" in this section with reference to the debt securities, we are also referring to "premium, if any."

We may from time to time, without notice to or the consent of the holders of any series of debt securities, create and issue further debt securities of any such series ranking equally with the debt securities of such series in all respects (or in all respects other than (1) the payment of interest accruing prior to the issue date of such further debt securities or (2) the first payment of interest following the issue date of such further debt securities). Such further debt securities may be consolidated and form a single series with the debt securities of such series and have the same terms as to status, redemption or otherwise as the debt securities of such series.

You may present debt securities for exchange and you may present debt securities for transfer in the manner, at the places and subject to the restrictions set forth in the debt securities and the applicable prospectus supplement. We will provide you those services without charge, although you may have to pay any tax or other governmental charge payable in connection with any exchange or transfer, as set forth in the indenture.

Debt securities may bear interest at a fixed rate or a floating rate. Debt securities bearing no interest or interest at a rate that at the time of issuance is below the prevailing market rate (original issue discount securities) may be sold at a discount below their stated principal amount. U.S. federal income tax considerations applicable to any such discounted debt securities or to certain debt securities issued at par which are treated as having been issued at a discount for U.S. federal income tax purposes will be described in the applicable prospectus supplement.

We may issue debt securities with the principal amount payable on any principal payment date, or the amount of interest payable on any interest payment date, to be determined by reference to one or more currency exchange rates, securities or baskets of securities, commodity prices or indices. You may receive a payment of principal on any principal payment date, or a payment of interest on any interest payment date, that is greater than or less than the amount of principal or interest otherwise payable on such dates, depending on the value on such dates of the applicable currency, security or basket of securities, commodity or index. Information as to the methods for determining the amount of principal or interest payable on any date, the currencies, securities or baskets of securities, commodities or indices to which the amount payable on such date is linked and certain related tax considerations will be set forth in the applicable prospectus supplement.

Certain Terms of the Senior Debt Securities

Covenants. Unless we indicate otherwise in a prospectus supplement, the senior debt securities will not contain any financial or restrictive covenants, including covenants restricting either us or any of our subsidiaries from incurring, issuing, assuming or guaranteeing any indebtedness secured by a lien on any of our or our subsidiaries' property or capital stock, or restricting either us or any of our subsidiaries from entering into sale and leaseback transactions.

Consolidation, Merger and Sale of Assets. Unless we indicate otherwise in a prospectus supplement, we may not consolidate with or merge into any other person, in a transaction in which we are not the surviving corporation, or convey, transfer or lease our properties and assets substantially as an entirety to any person, in either case, unless:

- the successor entity, if any, is a U.S. corporation, limited liability company, partnership or trust (subject to certain exceptions provided for in the senior indenture);
- the successor entity assumes our obligations on the senior debt securities and under the senior indenture;
- immediately after giving effect to the transaction, no default or event of default shall have occurred and be continuing; and
- certain other conditions are met.

No Protection in the Event of a Change in Control. Unless we indicate otherwise in a prospectus supplement with respect to a particular series of senior debt securities, the senior debt securities will not contain any provisions that may afford holders of the senior debt securities protection in the event we have a change in control or in the event of a highly leveraged transaction (whether or not such transaction results in a change in control).

Events of Default. Unless we indicate otherwise in a prospectus supplement with respect to a particular series of senior debt securities, the following are events of default under the senior indenture for any series of senior debt securities:

- failure to pay interest on any senior debt securities of such series when due and payable, if that default continues for a period of 30 days (or such other period as may be specified for such series);
- failure to pay principal on the senior debt securities of such series when due and payable whether at maturity, upon redemption, by declaration or otherwise (and, if specified for such series, the continuance of such failure for a specified period);
- default in the performance of or breach of any of our covenants or agreements in the senior indenture applicable to senior debt securities of such series, other than a covenant breach which is specifically dealt with elsewhere in the senior indenture, and that default or breach continues for a period of 90 days after we receive written notice from the trustee or from the holders of 25% or more in aggregate principal amount of the senior debt securities of such series;

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- certain events of bankruptcy or insolvency, whether or not voluntary; and
- any other event of default provided for in such series of senior debt securities as may be specified in the applicable prospectus supplement.

The default by us under any other debt, including any other series of debt securities, is not a default under the senior indenture.

If an event of default other than an event of default specified in the fourth bullet point above occurs with respect to a series of senior debt securities and is continuing under the senior indenture, then, and in each such case, either the trustee or the holders of not less than 25% in aggregate principal amount of such series then outstanding under the senior indenture (each such series voting as a separate class) by written notice to us and to the trustee, if such notice is given by the holders, may, and the trustee at the request of such holders shall, declare the principal amount of and accrued interest on such series of senior debt securities to be immediately due and payable, and upon this declaration, the same shall become immediately due and payable.

If an event of default specified in the fourth bullet point above occurs and is continuing, the entire principal amount of and accrued interest on each series of senior debt securities then outstanding shall become immediately due and payable.

Unless otherwise specified in the prospectus supplement relating to a series of senior debt securities originally issued at a discount, the amount due upon acceleration shall include only the original issue price of the senior debt securities, the amount of original issue discount accrued to the date of acceleration and accrued interest, if any.

Upon certain conditions, declarations of acceleration may be rescinded and annulled and past defaults may be waived by the holders of a majority in aggregate principal amount of all the senior debt securities of such series affected by the default, each series voting as a separate class. Furthermore, subject to various provisions in the senior indenture, the holders of a majority in aggregate principal amount of a series of senior debt securities, by notice to the trustee, may waive an existing default or event of default with respect to such senior debt securities and its consequences, except a default in the payment of principal of or interest on such senior debt securities or in respect of a covenant or provision of the senior indenture which cannot be modified or amended without the consent of the holders of each such senior debt security. Upon any such waiver, such default shall cease to exist, and any event of default with respect to such senior debt securities shall be deemed to have been cured, for every purpose of the senior indenture; but no such waiver shall extend to any subsequent or other default or event of default or impair any right consequent thereto.

The holders of a majority in aggregate principal amount of a series of senior debt securities may direct the time, method and place of conducting any proceeding for any remedy available to the trustee or exercising any trust or power conferred on the trustee with respect to such senior debt securities. However, the trustee may refuse to follow any direction that conflicts with law or the senior indenture, that may involve the trustee in personal liability or that the trustee determines in good faith may be unduly prejudicial to the rights of holders of such series of senior debt securities not joining in the giving of such direction and may take any other action it deems proper that is not inconsistent with any such direction received from holders of such series of senior debt securities. A holder may not pursue any remedy with respect to the senior indenture or any series of senior debt securities unless:

- the holder gives the trustee written notice of a continuing event of default;
- the holders of at least 25% in aggregate principal amount of such series of senior debt securities make a written request to the trustee to pursue the remedy in respect of such event of default;

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- the requesting holder or holders offer the trustee indemnity satisfactory to the trustee against any costs, liability or expense;
- the trustee does not comply with the request within 60 days after receipt of the request and the offer of indemnity; and
- during such 60-day period, the holders of a majority in aggregate principal amount of such series of senior debt securities do not give the trustee a direction that is inconsistent with the request.

These limitations, however, do not apply to the right of any holder of a senior debt security to receive payment of the principal of and interest on such senior debt security in accordance with the terms of such debt security, or to bring suit for the enforcement of any such payment in accordance with the terms of such debt security, on or after the due date for the senior debt securities, which right shall not be impaired or affected without the consent of the holder.

The senior indenture requires certain of our officers to certify, on or before a fixed date in each year in which any senior debt security is outstanding, as to their knowledge of our compliance with all covenants, agreements and conditions under the senior indenture.

Satisfaction and Discharge. We can satisfy and discharge our obligations to holders of any series of debt securities if:

- we pay or cause to be paid, as and when due and payable, the principal of and any interest on all senior debt securities of such series outstanding under the senior indenture; or
- all senior debt securities of such series have become due and payable or will become due and payable within one year (or are to be called for redemption within one year) and we deposit in trust a combination of cash and U.S. government or U.S. government agency obligations that will generate enough cash to make interest, principal and any other payments on the debt securities of that series on their various due dates.

Under current U.S. federal income tax law, the deposit and our legal release from the debt securities would be treated as though we took back your debt securities and gave you your share of the cash and debt securities or bonds deposited in trust. In that event, you could recognize gain or loss on the debt securities you give back to us. Purchasers of the debt securities should consult their own advisers with respect to the tax consequences to them of such deposit and discharge, including the applicability and effect of tax laws other than the U.S. federal income tax law.

Defeasance. Unless the applicable prospectus supplement provides otherwise, the following discussion of legal defeasance and discharge and covenant defeasance will apply to any series of debt securities issued under the indentures.

Legal Defeasance. We can legally release ourselves from any payment or other obligations on the debt securities of any series (called "legal defeasance") if certain conditions are met, including the following:

- We deposit in trust for your benefit and the benefit of all other direct holders of the debt securities of the same series a combination of cash and U.S. government or U.S. government agency obligations that will generate enough cash to make interest, principal and any other payments on the debt securities of that series on their various due dates.
- There is a change in current U.S. federal income tax law or an IRS ruling that lets us make the above deposit without causing you to be taxed on the debt securities any differently than if we did not make the deposit and instead repaid the debt securities ourselves when due. Under current U.S. federal income tax law, the deposit and our legal release from the debt securities would be treated as though we took back your debt securities and gave you your share of the

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cash and debt securities or bonds deposited in trust. In that event, you could recognize gain or loss on the debt securities you give back to us.

- We deliver to the trustee a legal opinion of our counsel confirming the tax law change or ruling described above.

If we accomplish legal defeasance, as described above, you would have to rely solely on the trust deposit for repayment of the debt securities. You could not look to us for repayment in the event of any shortfall.

Covenant Defeasance. Without any change of current U.S. federal tax law, we can make the same type of deposit described above and be released from some of the covenants in the debt securities (called "covenant defeasance"). In that event, you would lose the protection of those covenants but would gain the protection of having money and securities set aside in trust to repay the debt securities. In order to achieve covenant defeasance, we must do the following (among other things):

- We must deposit in trust for your benefit and the benefit of all other direct holders of the debt securities of the same series a combination of cash and U.S. government or U.S. government agency obligations that will generate enough cash to make interest, principal and any other payments on the debt securities of that series on their various due dates.
- We must deliver to the trustee a legal opinion of our counsel confirming that under current U.S. federal income tax law we may make the above deposit without causing you to be taxed on the debt securities any differently than if we did not make the deposit and instead repaid the debt securities ourselves when due.

If we accomplish covenant defeasance, you could still look to us for repayment of the debt securities if there were a shortfall in the trust deposit. In fact, if one of the events of default occurred (such as our bankruptcy) and the debt securities become immediately due and payable, there may be such a shortfall. Depending on the events causing the default, you may not be able to obtain payment of the shortfall.

Modification and Waiver. We and the trustee may amend or supplement the senior indenture or the senior debt securities without the consent of any holder:

- to convey, transfer, assign, mortgage or pledge any assets as security for the senior debt securities of one or more series;
- to evidence the succession of a corporation, limited liability company, partnership or trust to us, and the assumption by such successor of our covenants, agreements and obligations under the senior indenture or to otherwise comply with the covenant relating to mergers, consolidations and sales of assets;
- to comply with requirements of the SEC in order to effect or maintain the qualification of the senior indenture under the Trust Indenture Act of 1939, as amended;
- to add to our covenants such new covenants, restrictions, conditions or provisions for the protection of the holders, and to make the occurrence, or the occurrence and continuance, of a default in any such additional covenants, restrictions, conditions or provisions an event of default;
- to cure any ambiguity, defect or inconsistency in the senior indenture or in any supplemental indenture or to conform the senior indenture or the senior debt securities to the description of senior debt securities of such series set forth in this prospectus or any applicable prospectus supplement;
- to provide for or add guarantors with respect to the senior debt securities of any series;
- to establish the form or forms or terms of the senior debt securities as permitted by the senior indenture;

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- to evidence and provide for the acceptance of appointment under the senior indenture by a successor trustee, or to make such changes as shall be necessary to provide for or facilitate the administration of the trusts in the senior indenture by more than one trustee;
- to add to, delete from or revise the conditions, limitations and restrictions on the authorized amount, terms, purposes of issue, authentication and delivery of any series of senior debt securities;
- to make any change to the senior debt securities of any series so long as no senior debt securities of such series are outstanding; or
- to make any change that does not adversely affect the rights of any holder in any material respect.

Other amendments and modifications of the senior indenture or the senior debt securities issued may be made, and our compliance with any provision of the senior indenture with respect to any series of senior debt securities may be waived, with the consent of the holders of a majority of the aggregate principal amount of the outstanding senior debt securities of all series affected by the amendment or modification (voting together as a single class); provided, however, that each affected holder must consent to any modification, amendment or waiver that:

- extends the final maturity of any senior debt securities of such series;
- reduces the principal amount of any senior debt securities of such series;
- reduces the rate or extends the time of payment of interest on any senior debt securities of such series;
- reduces the amount payable upon the redemption of any senior debt securities of such series;
- changes the currency of payment of principal of or interest on any senior debt securities of such series;
- reduces the principal amount of original issue discount securities payable upon acceleration of maturity or the amount provable in bankruptcy;
- waives an uncured default in the payment of principal of or interest on the senior debt securities (except in the case of a rescission of acceleration as described above);
- changes the provisions relating to the waiver of past defaults or changes or impairs the right of holders to receive payment or to institute suit for the enforcement of any payment or conversion of any senior debt securities of such series on or after the due date therefor;
- modifies any of the provisions of these restrictions on amendments and modifications, except to increase any required percentage or to provide that certain other provisions cannot be modified or waived without the consent of the holder of each senior debt security of such series affected by the modification; or
- reduces the above-stated percentage of outstanding senior debt securities of such series whose holders must consent to a supplemental indenture or modifies or amends or waives certain provisions of or defaults under the senior indenture.

It shall not be necessary for the holders to approve the particular form of any proposed amendment, supplement or waiver, but it shall be sufficient if the holders' consent approves the substance thereof. After an amendment, supplement or waiver of the senior indenture in accordance with the provisions described in this section becomes effective, the trustee must give to the holders affected thereby certain notice briefly describing the amendment, supplement or waiver. Any failure by the trustee to give such notice, or any defect therein, shall not, however, in any way impair or affect the validity of any such amendment, supplemental indenture or waiver.

No Personal Liability of Incorporators, Stockholders, Officers, Directors. The senior indenture provides that no recourse shall be had under any obligation, covenant or agreement of ours in the senior indenture or any supplemental indenture, or in any of the senior debt securities or because of

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the creation of any indebtedness represented thereby, against any of our incorporators, stockholders, officers or directors, past, present or future, or of any predecessor or successor entity thereof under any law, statute or constitutional provision or by the enforcement of any assessment or by any legal or equitable proceeding or otherwise. Each holder, by accepting the senior debt securities, waives and releases all such liability.

Concerning the Trustee. The senior indenture provides that, except during the continuance of an event of default, the trustee will not be liable except for the performance of such duties as are specifically set forth in the senior indenture. If an event of default has occurred and is continuing, the trustee will exercise such rights and powers vested in it under the senior indenture and will use the same degree of care and skill in its exercise as a prudent person would exercise under the circumstances in the conduct of such person's own affairs.

The senior indenture and the provisions of the Trust Indenture Act of 1939 incorporated by reference therein contain limitations on the rights of the trustee thereunder, should it become a creditor of ours or any of our subsidiaries, to obtain payment of claims in certain cases or to realize on certain property received by it in respect of any such claims, as security or otherwise. The trustee is permitted to engage in other transactions, provided that if it acquires any conflicting interest (as defined in the Trust Indenture Act), it must eliminate such conflict or resign.

We may have normal banking relationships with the senior trustee in the ordinary course of business.

Unclaimed Funds. All funds deposited with the trustee or any paying agent for the payment of principal, premium, interest or additional amounts in respect of the senior debt securities that remain unclaimed for two years after the date upon which such principal, premium or interest became due and payable will be repaid to us. Thereafter, any right of any holder of senior debt securities to such funds shall be enforceable only against us, and the trustee and paying agents will have no liability therefor.

Governing Law. The senior indenture and the senior debt securities will be governed by, and construed in accordance with, the internal laws of the State of New York.

Certain Terms of the Subordinated Debt Securities

Other than the terms of the subordinated indenture and subordinated debt securities relating to subordination or otherwise as described in the prospectus supplement relating to a particular series of subordinated debt securities, the terms of the subordinated indenture and subordinated debt securities are identical in all material respects to the terms of the senior indenture and senior debt securities.

Additional or different subordination terms may be specified in the prospectus supplement applicable to a particular series.

Subordination. The indebtedness evidenced by the subordinated debt securities is subordinate to the prior payment in full of all of our senior indebtedness, as defined in the subordinated indenture. During the continuance beyond any applicable grace period of any default in the payment of principal, premium, interest or any other payment due on any of our senior indebtedness, we may not make any payment of principal or interest on the subordinated debt securities (except for certain sinking fund payments). In addition, upon any payment or distribution of our assets upon any dissolution, winding-up, liquidation or reorganization, the payment of the principal of and interest on the subordinated debt securities will be subordinated to the extent provided in the subordinated indenture in right of payment to the prior payment in full of all our senior indebtedness. Because of this subordination, if we dissolve or otherwise liquidate, holders of our subordinated debt securities may receive less, ratably, than holders of our senior indebtedness. The subordination provisions do not prevent the occurrence of an event of default under the subordinated indenture.

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The term "senior indebtedness" of a person means with respect to such person the principal of, premium, if any, interest on, and any other payment due pursuant to any of the following, whether outstanding on the date of the subordinated indenture or incurred by that person in the future:

- all of the indebtedness of that person for money borrowed;
- all of the indebtedness of that person evidenced by notes, debentures, bonds or other securities sold by that person for money;
- all of the lease obligations that are capitalized on the books of that person in accordance with generally accepted accounting principles;
- all indebtedness of others of the kinds described in the first two bullet points above and all lease obligations of others of the kind described in the third bullet point above that the person, in any manner, assumes or guarantees or that the person in effect guarantees through an agreement to purchase, whether that agreement is contingent or otherwise; and
- all renewals, extensions or refundings of indebtedness of the kinds described in the first, second or fourth bullet point above and all renewals or extensions of leases of the kinds described in the third or fourth bullet point above;

unless, in the case of any particular indebtedness, renewal, extension or refunding, the instrument creating or evidencing it or the assumption or guarantee relating to it expressly provides that such indebtedness, renewal, extension or refunding is not superior in right of payment to the subordinated debt securities. Our senior debt securities constitute senior indebtedness for purposes of the subordinated debt indenture.

DESCRIPTION OF CAPITAL STOCK

General

Our authorized capital stock consists of 200,000,000 shares of common stock, par value \$0.001 per share, and 10,000,000 shares of preferred stock, par value \$0.001 per share, all of which preferred stock is undesignated. The following description of our capital stock and provisions of our restated certificate of incorporation and amended and restated bylaws are summaries and are qualified by reference to our restated certificate of incorporation and our amended and restated bylaws, copies of which are filed with the SEC as exhibits to our registration statement of which this prospectus forms a part.

Common Stock

Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. An election of directors by our stockholders is determined by a plurality of the votes cast by the stockholders entitled to vote on the election. Other matters are decided by the affirmative vote of our stockholders having a majority in voting power of the votes cast by the stockholders present or represented and voting on such matter, except as otherwise disclosed below. Holders of common stock are entitled to receive proportionately any dividends as may be declared by our board of directors, subject to any preferential dividend rights of outstanding preferred stock.

In the event of our liquidation or dissolution, the holders of common stock are entitled to receive proportionately all assets available for distribution to stockholders after the payment of all debts and other liabilities and subject to the prior rights of any outstanding preferred stock. Holders of common stock have no preemptive, subscription, redemption or conversion rights. The rights, preferences and privileges of holders of common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future.

Preferred Stock

Under the terms of our restated certificate of incorporation, our board of directors is authorized to issue shares of preferred stock in one or more series without stockholder approval. Our board of directors has the discretion to determine the rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences, of each series of preferred stock.

The purpose of authorizing our board of directors to issue preferred stock and determine its rights and preferences is to eliminate delays associated with a stockholder vote on specific issuances. The issuance of preferred stock, while providing flexibility in connection with possible acquisitions, future financings and other corporate purposes, could have the effect of making it more difficult for a third party to acquire, or could discourage a third party from seeking to acquire, a majority of our outstanding voting stock. There are no shares of preferred stock currently outstanding.

Registration Rights

Amended and Restated Investors' Rights Agreement

The amended and restated investors' rights agreement, dated as of October 9, 2014, as amended, which we refer to as our investors' rights agreement, by and among our company and certain of our stockholders, provides specified holders of our previously outstanding preferred stock, including some of our directors and 5% stockholders and their respective affiliates and entities affiliated with our officers and directors, the right to require us to register the shares of common stock that were issued upon conversion of the preferred stock under the Securities Act under specified circumstances as described below. After registration pursuant to these rights, these shares will become freely tradable without restriction under the Securities Act.

Demand Registration Rights

Subject to specified limitations set forth in our investors' rights agreement, at any time the holders of 25% of then outstanding registrable securities, as defined in the investor's rights agreement, acting together, may demand in writing that we register their registrable securities under the Securities Act so long as the total amount of registrable shares requested to be registered has an anticipated aggregate offering price to the public, net of selling expenses, as defined in the investors' rights agreement, that would exceed \$5.0 million. We are not obligated to effect a registration statement pursuant to this demand provision on more than two occasions, subject to specified exceptions.

In addition, at any time that we are eligible to file a registration statement on Form S-3 under the Securities Act, subject to specified limitations, the holders of at least 25% of the registrable securities then outstanding may demand in writing that we register on Form S-3 registrable shares held by them so long as the total amount of registrable shares requested to be registered has an anticipated aggregate offering price to the public, net of selling expenses, as defined in the investors' rights agreement, of at least \$2.0 million. We are not obligated to effect a registration statement pursuant to this demand provision on more than two occasions in any twelve-month period, subject to specified exceptions.

Incidental Registration Rights

If, at any time, we propose to file a registration statement to register any of our securities under the Securities Act, either for our own account or for the account of any of our stockholders that are not holders of registrable shares, solely for cash and on a form that would also permit the registration of registrable shares, the holders of our registrable shares are entitled to notice of registration and, subject to specified exceptions, we will be required to register the registrable shares then held by them that they request that we register.

Expenses

Pursuant to the investor's rights agreement, we are required to pay all registration expenses, including registration fees, printing expenses, fees and disbursements of our counsel and accountants and reasonable fees and disbursements of one counsel representing the selling stockholders, other than any underwriting discounts and commissions, related to any demand or incidental registration. The investor's rights agreement contains customary cross-indemnification provisions, pursuant to which we are obligated to indemnify the selling stockholders in the event of material misstatements or omissions in the registration statement attributable to us, and they are obligated to indemnify us for material misstatements or omissions in the registration statement attributable to them.

Anti-Takeover Effects of Delaware Law and Our Charter and Bylaws

Delaware law and our restated certificate of incorporation and our amended and restated bylaws contain provisions that could have the effect of delaying, deferring or discouraging another party from acquiring control of us. These provisions, which are summarized below, are expected to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to encourage persons seeking to acquire control of us to first negotiate with our board of directors.

Staggered Board; Removal of Directors

Our restated certificate of incorporation and our amended and restated bylaws divide our board of directors into three classes with staggered three-year terms. In addition, a director may only be removed for cause and only by the affirmative vote of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast in an annual election of directors. Any vacancy on our board of directors, including a vacancy resulting from an enlargement of our board of directors, may only be filled by vote of a majority of our directors then in office. The classification of our board of directors and the limitations on the removal of directors and filling of vacancies could make it more difficult for a third party to acquire, or discourage a third party from seeking to acquire, control of our company.

Stockholder Action by Written Consent; Special Meetings

Our restated certificate of incorporation provides that any action required or permitted to be taken by our stockholders must be effected at a duly called annual or special meeting of such holders and may not be effected by any consent in writing by such holders. Our restated certificate of incorporation and our amended and restated bylaws also provide that, except as otherwise required by law, special meetings of our stockholders can only be called by our chairman of the board, our chief executive officer or our board of directors.

Advance Notice Requirements for Stockholder Proposals

Our amended and restated bylaws establish an advance notice procedure for stockholder proposals to be brought before an annual meeting of stockholders, including proposed nominations of persons for election to our board of directors. Stockholders at an annual meeting may only consider proposals or nominations specified in the notice of meeting or brought before the meeting by or at the direction of our board of directors or by a stockholder of record on the record date for the meeting who is entitled to vote at the meeting and who has delivered timely written notice in proper form to our secretary of the stockholder's intention to bring such business before the meeting. These provisions could have the effect of delaying until the next stockholder meeting stockholder actions that are favored by the holders of a majority of our outstanding voting securities.

Delaware Business Combination Statute

We are subject to Section 203 of the General Corporation Law of the State of Delaware. Subject to certain exceptions, Section 203 prevents a publicly held Delaware corporation from engaging in a "business combination" with any "interested stockholder" for three years following the date that the person became an interested stockholder, unless the interested stockholder attained such status with the approval of our board of directors or unless the business combination is approved in a prescribed manner. A "business combination" includes, among other things, a merger or consolidation involving us and the "interested stockholder" and a sale involving us and the "interested stockholder" of 10% or more of our assets. In general, an "interested stockholder" is any entity or person beneficially owning 15% or more of our outstanding voting stock and any entity or person affiliated with or controlling or controlled by such entity or person.

Amendment of Certificate of Incorporation and Bylaws

The General Corporation Law of the State of Delaware provides generally that the affirmative vote of a majority of the shares entitled to vote on any matter is required to amend a corporation's certificate of incorporation or bylaws, unless a corporation's certificate of incorporation or bylaws, as the case may be, requires a greater percentage. Our bylaws may be amended or repealed by a majority vote of our board of directors or by the affirmative vote of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast in any annual election of directors. In addition, the affirmative vote of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast in any annual election of directors is required to amend or repeal or to adopt any provisions inconsistent with any of the provisions of our certificate of incorporation described above under "—Staggered Board; Removal of Directors" and "—Stockholder Action by Written Consent; Special Meetings."

Listing on The NASDAQ Global Market

Our common stock is listed on The NASDAQ Global Market under the symbol "SYRS."

Authorized but Unissued Shares

The authorized but unissued shares of common stock and preferred stock are available for future issuance without stockholder approval, subject to any limitations imposed by the listing requirements of The NASDAQ Global Market. These additional shares may be used for a variety of corporate finance transactions, acquisitions and employee benefit plans. The existence of authorized but unissued and unreserved common stock and preferred stock could make it more difficult or discourage an attempt to obtain control of us by means of a proxy contest, tender offer, merger or otherwise.

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Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, N.A.

DESCRIPTION OF WARRANTS

We may issue warrants to purchase common stock, preferred stock or debt securities. We may offer warrants separately or together with one or more additional warrants, common stock, preferred stock or debt securities, or any combination of those securities in the form of units, as described in the applicable prospectus supplement. If we issue warrants as part of a unit, the accompanying prospectus supplement will specify whether those warrants may be separated from the other securities in the unit prior to the expiration date of the warrants. The applicable prospectus supplement will also describe the following terms of any warrants:

- the specific designation and aggregate number of, and the offering price at which we will issue, the warrants;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;
- the date on which the right to exercise the warrants will begin and the date on which that right will expire or, if you may not continuously exercise the warrants throughout that period, the specific date or dates on which you may exercise the warrants;
- whether the warrants are to be sold separately or with other securities as parts of units;
- whether the warrants will be issued in definitive or global form or in any combination of these forms, although, in any case, the form of a warrant included in a unit will correspond to the form of the unit and of any security included in that unit;
- any applicable material U.S. federal income tax consequences;
- the identity of the warrant agent for the warrants and of any other depositaries, execution or paying agents, transfer agents, registrars or other agents;
- the proposed listing, if any, of the warrants or any securities purchasable upon exercise of the warrants on any securities exchange;
- the designation and terms of any equity securities purchasable upon exercise of the warrants;
- the designation, aggregate principal amount, currency and terms of any debt securities that may be purchased upon exercise of the warrants;
- if applicable, the designation and terms of the preferred stock with which the warrants are issued and the number of warrants issued with each security;
- if applicable, the date from and after which any warrants issued as part of a unit and the related debt securities, preferred stock or common stock will be separately transferable;
- the number of shares of common stock or preferred stock purchasable upon exercise of a warrant and the price at which those shares may be purchased;
- if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;
- information with respect to book-entry procedures, if any;
- the anti-dilution provisions of, and other provisions for changes to or adjustment in the exercise price of, the warrants, if any;
- any redemption or call provisions; and
- any additional terms of the warrants, including terms, procedures and limitations relating to the exchange or exercise of the warrants.

DESCRIPTION OF UNITS

The following description, together with the additional information we may include in any applicable prospectus supplements, summarizes the material terms and provisions of the units that we may offer under this prospectus. While the terms summarized below will apply generally to any units that we may offer, we will describe the particular terms of any series of units in more detail in the applicable prospectus supplement. If we indicate in the prospectus supplement, the terms of any units offered under that prospectus supplement may differ from the terms described below. Specific unit agreements will contain additional important terms and provisions and will be incorporated by reference as an exhibit to the registration statement that includes this prospectus.

General

We may issue units consisting of debt securities, common stock, preferred stock, or warrants for the purchase of debt securities, common stock and/or preferred stock in one or more series, in any combination. Each unit will be issued so that the holder of the unit is also the holder of each security included in the unit. Thus, the holder of a unit will have the rights and obligations of a holder of each included security. The unit agreement under which a unit is issued may provide that the securities included in the unit may not be held or transferred separately, at any time or at any time before a specified date.

We will describe in the applicable prospectus supplement the terms of the series of units being offered, including:

- the designation and terms of the units and of the securities comprising the units, including whether and under what circumstances those securities may be held or transferred separately;
- any provisions of the governing unit agreement that differ from those described below; and
- any provisions for the issuance, payment, settlement, transfer or exchange of the units or of the securities comprising the units.

We may issue units in such amounts and in such numbers of distinct series as we determine.

The provisions described in this section, as well as those described under "Description of Capital Stock" and "Description of Warrants" will apply to each unit, as applicable, and to any common stock, preferred stock or warrant included in each unit, as applicable.

Unit Agent

The name and address of the unit agent for any units we offer will be set forth in the applicable prospectus supplement.

Enforceability of Rights by Holders of Units

Each unit agent will act solely as our agent under the applicable unit agreement and will not assume any obligation or relationship of agency or trust with any holder of any unit. A single bank or trust company may act as unit agent for more than one series of units. A unit agent will have no duty or responsibility in case of any default by us under the applicable unit agreement or unit, including any duty or responsibility to initiate any proceedings at law or otherwise, or to make any demand upon us. Any holder of a unit may, without the consent of the related unit agent or the holder of any other unit, enforce by appropriate legal action its rights as holder under any security included in the unit.

FORMS OF SECURITIES

Each debt security, warrant and unit will be represented either by a certificate issued in definitive form to a particular investor or by one or more global securities representing the entire issuance of securities. Unless the applicable prospectus supplement provides otherwise, certificated securities in definitive form and global securities will be issued in registered form. Definitive securities name you or your nominee as the owner of the security, and in order to transfer or exchange these securities or to receive payments other than interest or other interim payments, you or your nominee must physically deliver the securities to the trustee, registrar, paying agent or other agent, as applicable. Global securities name a depository or its nominee as the owner of the debt securities, warrants or units represented by these global securities. The depository maintains a computerized system that will reflect each investor's beneficial ownership of the securities through an account maintained by the investor with its broker/dealer, bank, trust company or other representative, as we explain more fully below.

Global Securities

We may issue the debt securities, warrants and units in the form of one or more fully registered global securities that will be deposited with a depository or its nominee identified in the applicable prospectus supplement and registered in the name of that depository or nominee. In those cases, one or more global securities will be issued in a denomination or aggregate denominations equal to the portion of the aggregate principal or face amount of the securities to be represented by global securities. Unless and until it is exchanged in whole for securities in definitive registered form, a global security may not be transferred except as a whole by and among the depository for the global security, the nominees of the depository or any successors of the depository or those nominees.

If not described below, any specific terms of the depository arrangement with respect to any securities to be represented by a global security will be described in the prospectus supplement relating to those securities. We anticipate that the following provisions will apply to all depository arrangements.

Ownership of beneficial interests in a global security will be limited to persons, called participants, that have accounts with the depository or persons that may hold interests through participants. Upon the issuance of a global security, the depository will credit, on its book-entry registration and transfer system, the participants' accounts with the respective principal or face amounts of the securities beneficially owned by the participants. Any dealers, underwriters or agents participating in the distribution of the securities will designate the accounts to be credited. Ownership of beneficial interests in a global security will be shown on, and the transfer of ownership interests will be effected only through, records maintained by the depository, with respect to interests of participants, and on the records of participants, with respect to interests of persons holding through participants. The laws of some states may require that some purchasers of securities take physical delivery of these securities in definitive form. These laws may impair your ability to own, transfer or pledge beneficial interests in global securities.

So long as the depository, or its nominee, is the registered owner of a global security, that depository or its nominee, as the case may be, will be considered the sole owner or holder of the securities represented by the global security for all purposes under the applicable indenture, warrant agreement or unit agreement. Except as described below, owners of beneficial interests in a global security will not be entitled to have the securities represented by the global security registered in their names, will not receive or be entitled to receive physical delivery of the securities in definitive form and will not be considered the owners or holders of the securities under the applicable indenture, warrant agreement or unit agreement. Accordingly, each person owning a beneficial interest in a global security

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must rely on the procedures of the depositary for that global security and, if that person is not a participant, on the procedures of the participant through which the person owns its interest, to exercise any rights of a holder under the applicable indenture, warrant agreement or unit agreement. We understand that under existing industry practices, if we request any action of holders or if an owner of a beneficial interest in a global security desires to give or take any action that a holder is entitled to give or take under the applicable indenture, warrant agreement or unit agreement, the depositary for the global security would authorize the participants holding the relevant beneficial interests to give or take that action, and the participants would authorize beneficial owners owning through them to give or take that action or would otherwise act upon the instructions of beneficial owners holding through them.

Principal, premium, if any, and interest payments on debt securities, and any payments to holders with respect to warrants or units, represented by a global security registered in the name of a depositary or its nominee will be made to the depositary or its nominee, as the case may be, as the registered owner of the global security. None of us, or any trustee, warrant agent, unit agent or other agent of ours, or any agent of any trustee, warrant agent or unit agent will have any responsibility or liability for any aspect of the records relating to payments made on account of beneficial ownership interests in the global security or for maintaining, supervising or reviewing any records relating to those beneficial ownership interests.

We expect that the depositary for any of the securities represented by a global security, upon receipt of any payment to holders of principal, premium, interest or other distribution of underlying securities or other property on that registered global security, will immediately credit participants' accounts in amounts proportionate to their respective beneficial interests in that global security as shown on the records of the depositary. We also expect that payments by participants to owners of beneficial interests in a global security held through participants will be governed by standing customer instructions and customary practices, as is now the case with the securities held for the accounts of customers or registered in "street name," and will be the responsibility of those participants.

If the depositary for any of the securities represented by a global security is at any time unwilling or unable to continue as depositary or ceases to be a clearing agency registered under the Exchange Act, and a successor depositary registered as a clearing agency under the Exchange Act is not appointed by us within 90 days, we will issue securities in definitive form in exchange for the global security that had been held by the depositary. Any securities issued in definitive form in exchange for a global security will be registered in the name or names that the depositary gives to the relevant trustee, warrant agent, unit agent or other relevant agent of ours or theirs. It is expected that the depositary's instructions will be based upon directions received by the depositary from participants with respect to ownership of beneficial interests in the global security that had been held by the depositary.

PLAN OF DISTRIBUTION

We may sell securities:

- through underwriters;
- through dealers;
- through agents;
- directly to purchasers; or
- through a combination of any of these methods of sale.

In addition, we may issue the securities as a dividend or distribution or in a subscription rights offering to our existing security holders. This prospectus may be used in connection with any offering of our securities through any of these methods or other methods described in the applicable prospectus supplement.

We may directly solicit offers to purchase securities, or agents may be designated to solicit such offers. We will, in the prospectus supplement relating to such offering, name any agent that could be viewed as an underwriter under the Securities Act, and describe any commissions that we must pay. Any such agent will be acting on a best efforts basis for the period of its appointment or, if indicated in the applicable prospectus supplement, on a firm commitment basis.

The distribution of the securities may be effected from time to time in one or more transactions:

- at a fixed price, or prices, which may be changed from time to time;
- at market prices prevailing at the time of sale;
- at prices related to such prevailing market prices; or
- at negotiated prices.

Each prospectus supplement will describe the method of distribution of the securities and any applicable restrictions.

The prospectus supplement with respect to the securities of a particular series will describe the terms of the offering of the securities, including the following:

- the name of the agent or any underwriters;
- the public offering or purchase price and the proceeds we will receive from the sale of the securities;
- any discounts and commissions to be allowed or re-allowed or paid to the agent or underwriters;
- all other items constituting underwriting compensation;
- any discounts and commissions to be allowed or re-allowed or paid to dealers; and
- any exchanges on which the securities will be listed.

If any underwriters or agents are utilized in the sale of the securities in respect of which this prospectus is delivered, we will enter into an underwriting agreement or other agreement with them at the time of sale to them, and we will set forth in the prospectus supplement relating to such offering the names of the underwriters or agents and the terms of the related agreement with them.

If a dealer is utilized in the sale of the securities in respect of which this prospectus is delivered, we will sell such securities to the dealer, as principal. The dealer may then resell such securities to the public at varying prices to be determined by such dealer at the time of resale.

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If we offer securities in a subscription rights offering to our existing security holders, we may enter into a standby underwriting agreement with dealers, acting as standby underwriters. We may pay the standby underwriters a commitment fee for the securities they commit to purchase on a standby basis. If we do not enter into a standby underwriting arrangement, we may retain a dealer-manager to manage a subscription rights offering for us.

Remarketing firms, agents, underwriters, dealers and other persons may be entitled under agreements which they may enter into with us to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, and may be customers of, engage in transactions with or perform services for us in the ordinary course of business.

If so indicated in the applicable prospectus supplement, we will authorize underwriters or other persons acting as our agents to solicit offers by certain institutions to purchase securities from us pursuant to delayed delivery contracts providing for payment and delivery on the date stated in the prospectus supplement. Each contract will be for an amount not less than, and the aggregate amount of securities sold pursuant to such contracts shall not be less nor more than, the respective amounts stated in the prospectus supplement. Institutions with whom the contracts, when authorized, may be made include commercial and savings banks, insurance companies, pension funds, investment companies, educational and charitable institutions and other institutions, but shall in all cases be subject to our approval. Delayed delivery contracts will not be subject to any conditions except that:

- the purchase by an institution of the securities covered under that contract shall not at the time of delivery be prohibited under the laws of the jurisdiction to which that institution is subject; and
- if the securities are also being sold to underwriters acting as principals for their own account, the underwriters shall have purchased such securities not sold for delayed delivery. The underwriters and other persons acting as our agents will not have any responsibility in respect of the validity or performance of delayed delivery contracts.

Certain agents, underwriters and dealers, and their associates and affiliates may be customers of, have borrowing relationships with, engage in other transactions with, and/or perform services, including investment banking services, for us or one or more of our respective affiliates in the ordinary course of business.

In order to facilitate the offering of the securities, any underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the securities or any other securities the prices of which may be used to determine payments on such securities. Specifically, any underwriters may overallocate in connection with the offering, creating a short position for their own accounts. In addition, to cover overallocations or to stabilize the price of the securities or of any such other securities, the underwriters may bid for, and purchase, the securities or any such other securities in the open market. Finally, in any offering of the securities through a syndicate of underwriters, the underwriting syndicate may reclaim selling concessions allowed to an underwriter or a dealer for distributing the securities in the offering if the syndicate repurchases previously distributed securities in transactions to cover syndicate short positions, in stabilization transactions or otherwise. Any of these activities may stabilize or maintain the market price of the securities above independent market levels. Any such underwriters are not required to engage in these activities and may end any of these activities at any time.

Under Rule 15c6-1 of the Exchange Act, trades in the secondary market generally are required to settle in three business days, unless the parties to any such trade expressly agree otherwise. The applicable prospectus supplement may provide that the original issue date for your securities may be more than three scheduled business days after the trade date for your securities. Accordingly, in such a case, if you wish to trade securities on any date prior to the third business day before the original issue date for your securities, you will be required, by virtue of the fact that your securities initially are

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expected to settle more than three scheduled business days after the trade date for your securities, to make alternative settlement arrangements to prevent a failed settlement.

The securities may be new issues of securities and may have no established trading market. The securities may or may not be listed on a national securities exchange. We can make no assurance as to the liquidity of or the existence of trading markets for any of the securities.

LEGAL MATTERS

Unless the applicable prospectus supplement indicates otherwise, the validity of the securities in respect of which this prospectus is being delivered will be passed upon by Wilmer Cutler Pickering Hale and Dorr LLP. Any underwriters will also be advised about the validity of the securities and other legal matters by their own counsel, which will be named in the applicable prospectus supplement.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2016, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.



**8,667,333 Shares of Common Stock
Class A Warrants to Purchase 1,951,844
Shares of Common Stock**

PROSPECTUS SUPPLEMENT

Joint Book-Running Managers

Cowen

Piper Jaffray

Lead Manager

JMP Securities

Co-Manager

Roth Capital Partners

April 5, 2019
