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PROSPECTUS

2,592,591 Shares



Common Stock

This prospectus relates to resale, from time to time, of up to 2,592,591 shares of our common stock by the selling stockholders (which term, as used in this prospectus, includes pledgees, donees, transferees or other successors-in-interest) identified in this prospectus. The selling stockholders acquired the shares of our common stock in our April 2017 private placement.

We are not selling any securities under this prospectus and we will not receive any proceeds from the sale of the shares.

We have agreed to bear all of the expenses incurred in connection with the registration of these shares. The selling stockholders will pay or assume brokerage commissions and similar charges, if any, incurred for the sale of shares of our common stock.

The selling stockholders identified in this prospectus may offer the shares from time to time through public or private transactions at prevailing market prices, at prices related to prevailing market prices or at privately negotiated prices. For additional information on the methods of sale that may be used by the selling stockholders, see the section entitled "Plan of Distribution" on page 14. For a list of the selling stockholders, see the section entitled "Selling Stockholders" on page 12.

We may amend or supplement this prospectus from time to time by filing amendments or supplements as required. You should read the entire prospectus and any amendments or supplements carefully before you make your investment decision.

Our common stock is listed on the NASDAQ Global Market ("NASDAQ") under the symbol "SYRS." On May 12, 2017, the closing sale price of our common stock as reported on NASDAQ was \$14.56. You are urged to obtain current market quotations for the common stock.

We are an "emerging growth company" under applicable Securities and Exchange Commission rules and, as such, have elected to comply with certain reduced public company disclosure requirements for this prospectus and future filings. See "Prospectus Summary—Implications of Being an Emerging Growth Company."

Our business and investment in our common stock involve significant risks. These risks are described in the section titled "Risk Factors" beginning on page 4 of this prospectus.

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

The date of this prospectus is May 25, 2017

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You should rely only on the information contained or incorporated by reference in this prospectus. We have not authorized any other person to provide you with different information. If anyone provides you with different or inconsistent information, you should not rely on it. This prospectus may only be used where it is legal to offer and sell shares of our common stock. If it is against the law in any jurisdiction to make an offer to sell these shares, or to solicit an offer from someone to buy these shares, then this prospectus does not apply to any person in that jurisdiction, and no offer or solicitation is made by this prospectus to any such person. You should assume that the information appearing in this prospectus is accurate only as of the date on the front cover of this prospectus, regardless of the time of delivery of this prospectus or of any sale of common stock. Our business, financial condition, results of operations and prospects may have changed since such date. Information contained on our website is not a part of this prospectus.

PROSPECTUS SUMMARY

This summary highlights, and is qualified in its entirety by, the more detailed information included elsewhere in this prospectus or incorporated by reference. This summary does not contain all of the information that may be important to you. You should read and carefully consider the entire prospectus, especially the "Risk Factors" section of this prospectus, before deciding to invest in our common stock.

Overview

We are a biopharmaceutical company pioneering an understanding of the non-coding regulatory region of the genome controlling the activation and repression of genes. Our goal is to advance a new wave of medicines to control the expression of disease-driving genes. We have built a proprietary gene control platform designed to systematically and efficiently analyze this unexploited region of DNA in human disease tissue to identify and drug novel targets linked to genomically defined patient populations. Because gene expression is fundamental to the function of all cells, we believe that our gene control platform has broad potential to create medicines that achieve profound and durable benefit across therapeutic areas and a range of diseases. By focusing on genomically defined subsets of patients, we believe we can conduct efficient clinical trials with a higher likelihood of success. We are currently focused on developing treatments for cancer and immune-mediated diseases and are building a pipeline of gene control medicines.

In September 2016, we began enrolling patients in a Phase 2 clinical trial for our lead product candidate, SY-1425 (tamibarotene), an oral, potent and selective retinoic acid receptor alpha, or RAR α , agonist, in genomically defined subsets of patients with relapsed or refractory acute myelogenous leukemia, or AML, and relapsed high-risk myelodysplastic syndrome, or MDS. In the fourth quarter of 2016, an investigational device exemption for the assay being used to select patients for this trial was approved by the U.S. Food and Drug Administration. With this approval, we have expanded this trial to include newly diagnosed AML patients who are at least 60 years old and are not suitable candidates for standard chemotherapy, and lower-risk, transfusion-dependent MDS patients. During 2017, we further expanded this trial to explore the safety and efficacy of SY-1425 when combined with azacitidine, a hypomethylating agent that is commonly used to treat AML, in newly diagnosed AML patients who are at least 60 years old and not suitable candidates for standard chemotherapy. On the basis of preclinical data we have generated, we also plan to pursue clinical development of SY-1425 in combination with a therapeutic anti-CD38 antibody in defined subsets of AML and MDS patients identified using our biomarkers. In May 2017, we initiated a Phase 1 clinical trial for our development candidate SY-1365, a highly potent and selective small molecule inhibitor of cyclin-dependent kinase 7, or CDK7, in patients with advanced solid tumors. Both of these programs may have potential in additional disease indications. Using our platform, we are also generating a pipeline of novel preclinical drug candidates in cancer, including immuno-oncology, and advancing our research efforts in autoimmune and rare genetic diseases. We plan to advance one of our four preclinical programs to support a potential investigational new drug application, or IND, filing in 2019. Our goal is to build a fully integrated biopharmaceutical company based on our leadership position in gene control.

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. We have included our website address in this prospectus solely as an inactive textual reference.

Except as otherwise indicated herein or as the context otherwise requires, references in this prospectus to "Syros," "the company," "we," "us" and "our" refer to Syros Pharmaceuticals, Inc. and our wholly owned subsidiary Syros Securities Corporation.

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.

Implications of Being an Emerging Growth Company

As a company with less than \$1.0 billion of revenue during our last fiscal year, we qualify as an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. For so long as we remain an emerging growth company, we are permitted and intend to rely on certain exemptions from various public reporting requirements, including the requirement that our internal control over financial reporting be audited by our independent registered public accounting firm pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, certain requirements related to the disclosure of executive compensation in this prospectus and in our periodic reports and proxy statements, and the requirement that we hold a nonbinding advisory vote on executive compensation and any golden parachute payments. The JOBS Act also provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. We have irrevocably elected not to avail ourselves of this exemption and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies. Because we intend to rely on certain disclosure and other requirements of the JOBS Act, the information contained herein may be different than the information you receive from other public companies in which you hold stock. In addition, it is possible that some investors will find our common stock less attractive as a result of our determination to avail ourselves of exemptions under the JOBS Act, which may result in a less active trading market for our common stock and higher volatility in our stock price. We will remain an emerging growth company until the earlier to occur of: (1) the last day of the fiscal year in which we have total annual gross revenues of \$1.0 billion or more; (2) the last day of the fiscal year following the fifth anniversary of the date of the closing of our initial public offering; (3) the date on which we have issued more than \$1.0 billion in nonconvertible debt during the previous three years; or (4) the date on which we are deemed to be a large accelerated filer under the rules of the Securities and Exchange Commission.

THE OFFERING

Common stock offered by selling stockholders	2,592,591 shares
Use of proceeds	We will not receive any proceeds from the sale of shares in this offering.
Risk factors	You should read the "Risk Factors" section included or incorporated by reference in this prospectus for a discussion of factors to consider carefully before deciding to invest in shares of our common stock.
NASDAQ Global Market symbol	"SYRS"

DESCRIPTION OF PRIVATE PLACEMENT WITH THE SELLING STOCKHOLDERS

On April 20, 2017, we entered into a securities purchase agreement for a private placement with the selling stockholders whereby, on April 26, 2017 we issued and sold 2,592,591 shares of our common stock at a price of \$13.50 per share for gross proceeds of approximately \$35.0 million. For a detailed description of the transactions contemplated by the securities purchase agreement with the selling stockholders and the securities issued pursuant thereto, see the section captioned "Selling Stockholders" in this prospectus. We filed the registration statement on Form S-1, of which this prospectus forms a part, to fulfill our contractual obligations under the registration rights agreement entered into concurrently with the securities purchase agreement with the selling stockholders to provide for the resale by the selling stockholders of the shares of common stock offered hereby.

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 Securities and Exchange Commission, or 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.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS AND INDUSTRY DATA

This prospectus and the documents incorporated by reference herein contain forward-looking statements that involve substantial risks and uncertainties. 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 our clinical trials for SY-1425 and SY-1365;
- planned clinical trials for our product candidates, whether conducted by us or by any future collaborators, including the timing of these trials and of the anticipated results;
- our plans to research, develop, manufacture and commercialize our current and future product candidates;
- our plans to develop and seek approval of companion diagnostic tests for use in identifying patients who may benefit from treatment with our products and product candidates;
- our expectations regarding the potential benefits of our gene control platform and our approach;
- our plans to seek to enter into collaborations for the development and commercialization of certain product candidates;
- the potential benefits of any future collaboration;
- the timing of and our ability to obtain and maintain regulatory approvals for our product candidates;

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- 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
- 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.

USE OF PROCEEDS

We are filing the registration statement of which this prospectus is a part to permit holders of the shares of our common stock described in the section entitled "Selling Stockholders" to resell such shares. We are not selling any securities under this prospectus and we will not receive any proceeds from the sale of shares by the selling stockholders.

The selling stockholders will pay any underwriting discounts and commissions and expenses incurred by the selling stockholders for brokerage, accounting, tax or legal services or any other expenses incurred by the selling stockholders in disposing of the shares. We will bear all other costs, fees and expenses incurred in effecting the registration of the shares covered by this prospectus, including, without limitation, all registration and filing fees, NASDAQ listing fees and fees and expenses of our counsel and our accountants.

MARKET PRICE OF OUR COMMON STOCK

Our common stock has been listed on the NASDAQ Global Market under the symbol "SYRS" since June 30, 2016. Prior to that, there was no public market for our common stock. The following table sets forth for the periods indicated the high and low sales prices per share of our common stock as reported on NASDAQ:

<u>Year ending December 31, 2016</u>	<u>High</u>	<u>Low</u>
Second Quarter (beginning June 30, 2016):	\$ 19.80	\$ 14.58
Third Quarter:	\$ 21.50	\$ 8.16
Fourth Quarter:	\$ 16.85	\$ 11.31

<u>Year ending December 31, 2017</u>	<u>High</u>	<u>Low</u>
First Quarter:	\$ 16.74	\$ 10.22
Second Quarter (through May 12, 2017):	\$ 16.49	\$ 13.27

On May 12, 2017, the closing price for our common stock was \$14.56 per share. As of May 12, 2017, there were 61 holders of record of our common stock

DIVIDEND POLICY

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

DILUTION

This offering is for sales of common stock, if any, by the selling stockholders on a continuous or delayed basis in the future. Sales of common stock by the selling stockholders will not result in a change to the net tangible book value per share before and after the distribution of shares by such selling stockholders.

There will be no change in net tangible book value per share attributable to cash payments made by purchasers of the shares being offered. Prospective investors should be aware, however, that the price of shares of common stock may not bear any rational relationship to net tangible book value per share of the common stock.

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

Resale Registration Rights

Under the registration rights agreement for the April 2017 private placement, we have agreed to file the registration statement of which this prospectus is a part with the SEC, covering the resale of the 2,592,591 shares of common stock issued in such private placement.

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 after we become 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

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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."

Exclusive Forum Selection

Our restated certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware (or if the Court of Chancery does not have jurisdiction, the federal district court for the District of Delaware) shall be the sole and exclusive forum for (1) any derivative action or proceeding brought on behalf of our company, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers or employees to our company or our stockholders, (3) any action asserting a claim against our company arising pursuant to any provision of the General Corporation Law of the State of Delaware or our restated certificate of incorporation or amended and restated bylaws, or (4) any action asserting a claim against our company governed by the internal affairs doctrine. Although our restated certificate of incorporation contains the choice of forum provision described above, it is possible that a court could rule that such a provision is inapplicable for a particular claim or action or that such provision is unenforceable.

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.

Transfer Agent and Registrar

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

SELLING STOCKHOLDERS

On April 20, 2017, we entered into a securities purchase agreement, or the Purchase Agreement, with the selling stockholders, pursuant to which we issued and sold 2,592,591 shares of our common stock at a price of \$13.50 per share for gross proceeds of approximately \$35.0 million, which we refer to as the Private Placement.

In connection with the Private Placement, we entered into a registration rights agreement with the selling stockholders, dated as of April 20, 2017, or the Registration Rights Agreement, pursuant to which we agreed to file a registration statement with the SEC covering the resale of the shares of common stock sold in the Private Placement. We agreed to file such registration statement within 30 days of the closing of the Private Placement. The Registration Rights Agreement includes customary indemnification rights in connection with the registration statement. The registration statement of which this prospectus is a part has been filed in accordance with the Registration Rights Agreement.

The foregoing summary descriptions of the Purchase Agreement and the Registration Rights Agreement do not purport to be complete and are qualified in their entirety by reference to the full text of such documents, which were filed as exhibits to our Current Report on Form 8-K, dated April 20, 2017, and are incorporated by reference herein.

The table below sets forth, to our knowledge, information concerning the beneficial ownership of shares of our common stock by the selling stockholders as of April 26, 2017. The information in the table below with respect to the selling stockholders has been obtained from the selling stockholders. The selling stockholders may sell all, some or none of the shares of common stock subject to this prospectus. See "Plan of Distribution."

Beneficial ownership is determined in accordance with the rules of the SEC and includes voting or investment power with respect to shares. Unless otherwise indicated below, to our knowledge, all persons named in the table have sole voting and investment power with respect to their shares of common stock, except to the extent authority is shared by spouses under applicable law. The inclusion of any shares in this table does not constitute an admission of beneficial ownership for the person named below.

<u>Name of Selling Stockholder</u>	<u>Shares of Common Stock Beneficially Owned Prior to Offering</u>		<u>Number of Shares of Common Stock Being Offered</u>	<u>Shares of Common Stock to be Beneficially Owned After Offering(1)</u>	
	<u>Number</u>	<u>Percentage</u>		<u>Number</u>	<u>Percentage</u>
667, L.P.(2)	61,347	*	36,629	24,718	*
Baker Brothers Life Sciences, L.P.(2)	513,488	1.97%	333,741	179,747	*
Casdin Partners Master Fund LP(3)	231,215	*	74,074	157,141	*
Cormorant Global Healthcare Master Fund, LP(4)	246,459	*	246,459	—	*
CRMA SPV, L.P.(5)	49,837	*	49,837	—	*
Hawkes Bay Master Investors (Cayman) LP(9)	623,774	2.40%	623,774	—	*
Opaleye, L.P.(6)	99,223	*	74,074	25,149	*
Salthill Investors (Bermuda) L.P.(9)	64,541	*	64,541	—	*
Salthill Partners, L.P.(9)	144,573	*	144,573	—	*
Samsara BioCapital, L.P.(7)	740,740	2.85%	740,740	—	*
Special Situations Life Sciences Fund, L.P. (8)	121,624	*	74,074	47,550	*
Wellington Trust Company, National Association Multiple Collective Investment Funds Trust, Biotechnology Portfolio(9)	130,075	*	130,075	—	*

* Less than one percent.

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- (1) We do not know when or in what amounts a selling stockholder may offer shares for sale. The selling stockholders might not sell any or all of the shares offered by this prospectus. Because the selling stockholders may offer all or some of the shares pursuant to this offering, and because there are currently no agreements, arrangements or understandings with respect to the sale of any of the shares, we cannot estimate the number of the shares that will be held by the selling stockholders after completion of the offering. However, for purposes of this table, we have assumed that, after completion of the offering, none of the shares covered by this prospectus will be held by the selling stockholders.
- (2) Baker Bros. Advisors LP (the "Adviser") is the management company and investment adviser to each of Baker Brothers Life Sciences, L.P. and 667, L.P. (the "Funds"). The Adviser is the management company and investment adviser to the Funds and may be deemed to beneficially own all shares held by the Funds. Baker Bros. Advisors (GP) LLC (the "Adviser GP") is the sole general partner of the Adviser. Julian C. Baker and Felix J. Baker have voting and investment power over the shares held by each of the Funds, as principals of the Adviser GP. Julian C. Baker, Felix J. Baker, the Adviser and the Adviser GP disclaim beneficial ownership of all shares held by the Funds except to the extent their pecuniary interest therein.
- (3) Casdin Partners, L.P. is the beneficial owner of Casdin Partners Master Fund LP.
- (4) The sole general partner of Cormorant Global Healthcare Master Fund, LP (the "Fund") is Cormorant Global Healthcare GP, LLC (the "GP"). Bihua Chen is the sole managing member of the GP, and may be deemed to have sole voting and investment power of the securities held by the Fund. Bihua Chen disclaims beneficial ownership of such securities except to the extent of her pecuniary interests therein.
- (5) The sole investment manager of CRMA SPV, L.P. (the "Account") is Cormorant Asset Management, LLC (the "Manager"). Bihua Chen is the sole managing member of the Manager, and may be deemed to have sole voting and investment power of the securities held by the Account. Bihua Chen disclaims beneficial ownership of such securities except to the extent of her pecuniary interests therein.
- (6) James Silverman is the president of Opaleye Management Inc., the investment manager of Opaleye, L.P. and is deemed to have sole voting and investment power over the securities held by Opaleye, L.P. Mr. Silverman disclaims beneficial ownership of such securities, except to the extent of his pecuniary interest therein.
- (7) The general partner of Samsara BioCapital, L.P. (the "LP") is Samsara BioCapital GP, LLC (the "LLC"). The managers of the LLC are Srinivas Akkaraju and Michael Dybbs. These individuals may be deemed to have shared voting and investment power of the securities held by the LP.
- (8) Austin W. Marx, David M. Greenhouse and Adam C. Stettner are members of LS Advisers, LLC, the general partner of Special Situations Life Sciences Fund, L.P. AWM Investment Company, Inc. serves as the investment adviser to Special Situations Life Sciences Fund, L.P. Messrs. Marx, Greenhouse and Stettner share sole voting and investment power of the shares of common stock beneficially owned by Special Situations Life Sciences Fund, L.P.
- (9) Wellington Management Company LLP is the investment adviser to this entity. Wellington Management Company LLP is an investment adviser registered under the Investment Advisers Act of 1940, as amended, and is an indirect subsidiary of Wellington Management Group LLP. Wellington Management Company LLP and Wellington Management Group LLP may each be deemed to share beneficial ownership (within the meaning of Rule 13d-3 promulgated under the Exchange Act) of the shares indicated in the table, all of which are held of record by the entity named in the table or a nominee on its behalf. The business address of the entity named in the table is c/o Wellington Management Company LLP, 280 Congress Street, Boston, Massachusetts 02210. The business address of Wellington Management Company LLP and Wellington Management Group LLP is 280 Congress Street, Boston, Massachusetts 02210.

None of the selling stockholders has held any position or office, or has otherwise had a material relationship, with us or any of our subsidiaries within the past three years.

PLAN OF DISTRIBUTION

The shares covered by this prospectus may be offered and sold from time to time by the selling stockholders. The term "selling stockholders" includes donees, pledgees, transferees or other successors-in-interest selling shares received after the date of this prospectus from a selling stockholder as a gift, pledge, partnership distribution or other non-sale related transfer. The selling stockholders will act independently of us in making decisions with respect to the timing, manner and size of each sale. Such sales may be made on one or more exchanges or in the over-the-counter market or otherwise, at prices and under terms then prevailing or at prices related to the then current market price or in negotiated transactions. The selling stockholders may sell their shares by one or more of, or a combination of, the following methods:

- purchases by a broker-dealer as principal and resale by such broker-dealer for its own account pursuant to this prospectus;
- ordinary brokerage transactions and transactions in which the broker solicits purchasers;
- block trades in which the broker-dealer so engaged will attempt to sell the shares as agent but may position and resell a portion of the block as principal to facilitate the transaction;
- an over-the-counter distribution in accordance with the NASDAQ rules;
- in privately negotiated transactions; and
- in options transactions.

In addition, any shares that qualify for sale pursuant to Rule 144 may be sold under Rule 144 rather than pursuant to this prospectus.

To the extent required, this prospectus may be amended or supplemented from time to time to describe a specific plan of distribution. In connection with distributions of the shares or otherwise, the selling stockholders may enter into hedging transactions with broker-dealers or other financial institutions. In connection with such transactions, broker-dealers or other financial institutions may engage in short sales of the common stock in the course of hedging the positions they assume with selling stockholders. The selling stockholders may also sell the common stock short and redeliver the shares to close out such short positions. The selling stockholders may also enter into option or other transactions with broker-dealers or other financial institutions which require the delivery to such broker-dealer or other financial institution of shares offered by this prospectus, which shares such broker-dealer or other financial institution may resell pursuant to this prospectus (as supplemented or amended to reflect such transaction). The selling stockholders may also pledge shares to a broker-dealer or other financial institution, and, upon a default, such broker-dealer or other financial institution, may effect sales of the pledged shares pursuant to this prospectus (as supplemented or amended to reflect such transaction).

In effecting sales, broker-dealers or agents engaged by the selling stockholders may arrange for other broker-dealers to participate. Broker-dealers or agents may receive commissions, discounts or concessions from the selling stockholders in amounts to be negotiated immediately prior to the sale.

In offering the shares covered by this prospectus, the selling stockholders and any broker-dealers who execute sales for the selling stockholders may be deemed to be "underwriters" within the meaning of the Securities Act in connection with such sales. Any profits realized by the selling stockholders and the compensation of any broker-dealer may be deemed to be underwriting discounts and commissions.

In order to comply with the securities laws of certain states, if applicable, the shares must be sold in such jurisdictions only through registered or licensed brokers or dealers. In addition, in certain states the shares may not be sold unless they have been registered or qualified for sale in the applicable state or an exemption from the registration or qualification requirement is available and is complied with.

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We have advised the selling stockholders that the anti-manipulation rules of Regulation M under the Exchange Act may apply to sales of shares in the market and to the activities of the selling stockholders and their affiliates. In addition, we will make copies of this prospectus available to the selling stockholders for the purpose of satisfying the prospectus delivery requirements of the Securities Act. The selling stockholders may indemnify any broker-dealer that participates in transactions involving the sale of the shares against certain liabilities, including liabilities arising under the Securities Act.

At the time a particular offer of shares is made, if required, a prospectus supplement will be distributed that will set forth the number of shares being offered and the terms of the offering, including the name of any underwriter, dealer or agent, the purchase price paid by any underwriter, any discount, commission and other item constituting compensation, any discount, commission or concession allowed or reallocated or paid to any dealer, and the proposed selling price to the public.

We have agreed to indemnify the selling stockholders against certain liabilities, including certain liabilities under the Securities Act.

We have agreed with the selling stockholders to keep the registration statement of which this prospectus constitutes a part effective until the earlier of (i) such time as all of the shares covered by this prospectus have been disposed of pursuant to and in accordance with the registration statement or (ii) the date on which all of the shares may be sold without restriction pursuant to Rule 144 of the Securities Act.

LEGAL MATTERS

The validity of the shares of our common stock offered hereby is being passed upon for us by Wilmer Cutler Pickering Hale and Dorr LLP.

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.

WHERE YOU CAN FIND MORE INFORMATION

We file reports, proxy statements and other documents with the SEC. You may read and copy any document we file at the SEC's public reference room at 100 F Street, N.E., Room 1580, Washington, D.C. 20549. You should call 1-800-SEC-0330 for more information on the public reference room. Our SEC filings are also available to you on the SEC's Internet site at www.sec.gov.

This prospectus is part of a registration statement that we filed with the SEC. The registration statement contains more information than this prospectus regarding us and our common stock, 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 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. Information contained in this prospectus and information that we file with the SEC in the future and incorporate by reference in this prospectus 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 and prior to the sale of all the shares covered by this prospectus.

1. Our Annual Report on Form 10-K for the year ended December 31, 2016, filed with the SEC on March 20, 2017 (including information specifically incorporated by reference therein from our Proxy Statement filed with the SEC on April 25, 2017);
2. Our Quarterly Report on Form 10-Q for the quarter ended March 31, 2017, filed with the SEC on May 15, 2017;
3. Our Current Reports on Form 8-K filed with the SEC on January 9, 2017 (except Item 2.02), January 30, 2017, April 21, 2017 and April 26, 2017; and
4. Any other filings we make pursuant to the Exchange Act after the date of filing the initial registration statement and prior to effectiveness of the registration statement.

A statement contained in a document incorporated by reference into this prospectus shall be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus, any prospectus supplement or in any other subsequently filed document which is also incorporated in this prospectus 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.

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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 Officer & Secretary
Telephone: (617) 744-1340

2,592,591 Shares



Common Stock

PROSPECTUS

May 25, 2017
