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As filed with the Securities and Exchange Commission on February 2, 2018

Registration No. 333-222634

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

Pre-Effective Amendment
No.1 to
FORM S-3
REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

SYROS PHARMACEUTICALS, INC.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	45-3772460
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification Number)

**620 Memorial Drive, Suite 300
Cambridge, Massachusetts 02139
(617) 744-1340**

(Address, Including Zip Code, and Telephone Number, Including Area Code, of Registrant's Principal Executive Offices)

**Nancy Simonian, M.D.
President and Chief Executive Officer
Syros Pharmaceuticals, Inc.
620 Memorial Drive, Suite 300
Cambridge, Massachusetts 02139
(617) 744-1340**

(Name, Address, Including Zip Code, and Telephone Number, Including Area Code, of Agent for Service)

Copies to:

**Gerald E. Quirk
Chief Legal and Administrative Officer and
Secretary
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620 Memorial Drive, Suite 300
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Boston, Massachusetts 02109
Telephone: (617) 526-6000
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**Approximate date of commencement of proposed sale to the public:
From time to time after this registration statement becomes effective.**

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box.

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act

registration statement number of the earlier effective registration statement for the same offering.

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box.

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box.

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

Large accelerated filer

Accelerated filer

Non-accelerated filer

(Do not check if a
smaller reporting
company)

Smaller reporting company

Emerging growth
company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 7(a)(2)(B) of the Securities Act.

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities To Be Registered	Amount to be Registered(1)(2)	Proposed Maximum Offering Price Per Share(3)	Proposed Maximum Aggregate Offering Price(3)	Amount of Registration Fee(3)
Common Stock, \$0.001 par value per share	918,677	\$9.49	\$8,718,245	\$1,085.43

- (1) The shares will be offered for resale by a selling stockholder pursuant to the prospectus contained herein.
- (2) Pursuant to Rule 416 under the Securities Act, this registration statement also covers any additional number of shares of common stock issuable upon stock splits, stock dividends, or other distribution, recapitalization or similar events with respect to the shares of common stock being registered pursuant to this registration statement.
- (3) Estimated solely for purposes of calculating the registration fee pursuant to Rule 457(c) under the Securities Act, based on average of high and low price per share of the common stock as reported on the Nasdaq Global Select Market on January 31, 2018.

The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment which specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until the Registration Statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

The information in this prospectus is not complete and may be changed. The selling stockholder named in this prospectus may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and the selling stockholder named in this prospectus is not soliciting offers to buy these securities in any state or other jurisdiction where the offer or sale is not permitted.

Subject to completion, dated February 2, 2018

PROSPECTUS

918,677 Shares



Common Stock

This prospectus relates to the resale of up to 918,677 shares of our common stock by the selling stockholder listed on page 8, including its transferees, pledgees, donees, assignees or successors-in-interest, which shares were issued to the selling stockholder in a private placement. We are registering these shares on behalf of the selling stockholder, to be offered and sold by it from time to time.

We will not receive any proceeds from the sale of the shares.

The selling stockholder identified in this prospectus, or its pledgees, donees, transferees, assignees or other successors-in-interest, may offer the shares from time to time on terms to be determined at the time of sale through ordinary brokerage transactions or through any other means described in this prospectus under the caption "Plan of Distribution." The shares may be sold at fixed prices, at prevailing market prices, at prices related to prevailing market prices or at negotiated prices.

Our common stock is listed on the Nasdaq Global Select Market ("Nasdaq") under the symbol "SYRS." On February 1, 2018, the last reported closing sale price of our common stock on Nasdaq was \$9.53 per share.

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."

Investing in our common stock involves a high degree of risk. 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 _____, 2018.

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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.

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 in this prospectus. This summary does not contain all of the information that you should consider before investing. 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 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 genetic 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 that is being evaluated in combination with azacitidine, a hypomethylating agent, and with daratumumab, an anti-CD38 therapeutic antibody, 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. We also have multiple programs in earlier stages of research and development in oncology, including immuno-oncology, 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 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

We are an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. As a result, we may take advantage of reduced reporting requirements that are otherwise applicable to public companies, including delaying auditor attestation of internal control over financial reporting and reducing executive compensation disclosures. 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 \$1.07 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	918,677 shares
Terms of the offering	The selling stockholder, including its transferees, donees, pledgees, assignees or successors-in-interest, may sell, transfer or otherwise dispose of any or all of the shares of common stock offered by this prospectus from time to time on the Nasdaq Global Select Market or any other stock exchange, market or trading facility on which the shares are traded or in private transactions. The shares of common stock may be sold at fixed prices, at prevailing market prices, at prices related to prevailing market prices or at negotiated prices.
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 on page 4 of this prospectus for a discussion of factors to consider carefully before deciding to invest in shares of our common stock.
Nasdaq Global Select Market symbol	"SYRS"

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;
- whether the collaboration with Incyte Corporation, or Incyte, will yield any validated targets, whether Incyte will exercise any of its options to exclusively license any such targets, and whether and when any of the target validation fees, options exercise fees, milestone payments or royalties under the Incyte collaboration will ever be paid;
- the potential benefits of any future collaboration;
- the timing of and our ability to obtain and maintain regulatory approvals for our product candidates;
- the rate and degree of market acceptance and clinical utility of any products for which we receive marketing approval;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our intellectual property position and strategy;
- our ability to identify additional products or product candidates with significant commercial potential;
- our expectations related to the use of our current cash, cash equivalents and marketable securities and the period of time in which such capital will be sufficient to fund our planned operations;

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- 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 the holder of the shares of our common stock described in the section entitled "Selling Stockholder" 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 stockholder.

The selling stockholder will pay any underwriting discounts and commissions and expenses incurred by the selling stockholder for brokerage, accounting, tax or legal services or any other expenses incurred by the selling stockholder 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.

SELLING STOCKHOLDER

This prospectus relates to the possible sale by Incyte Corporation, or Incyte, who we refer to in this prospectus as the "selling stockholder," of up to 918,677 shares of our common stock (plus an indeterminate number of shares of our common stock that may be issued upon stock splits, stock dividends, or similar transactions, in accordance with Rule 416 under the Securities Act) that were issued to the selling stockholder on January 8, 2018 and February 2, 2018, pursuant to a stock purchase agreement, as amended. See "Relationship with Selling Stockholder" below for more information regarding the transaction to which these shares of common stock relate.

The table below sets forth, to our knowledge, information concerning the beneficial ownership of shares of our common stock by the selling stockholder as of February 2, 2018. The selling stockholder may sell all, some or none of the shares of common stock subject to this prospectus. See "Plan of Distribution."

The information in the table below with respect to the selling stockholder has been obtained from the selling stockholder, with beneficial ownership and percentage ownership determined in accordance with the rules and regulations of the SEC and including voting or investment power with respect to shares. Unless otherwise indicated below, to our knowledge, the person named in the table has sole voting and investment power with respect to such person's shares of common stock. The inclusion of any shares in this table does not constitute an admission of beneficial ownership for the person named below. The percentage of beneficial ownership is based upon 31,540,918 shares of common stock outstanding on February 2, 2018.

To our knowledge and except as noted under the caption titled "Relationship with Selling Stockholder" below, the selling stockholder does not have, and within the past three years has not had, any position, office or other material relationship with us or any of our predecessors or affiliates.

Name of Selling Stockholder	Shares of Common Stock Beneficially Owned Prior to Offering		Number of Shares of Common Stock Being Offered	Shares of Common Stock to be Beneficially Owned After Offering(1)	
	Number	Percentage		Number	Percentage
Incyte Corporation(2)	918,677	2.91%	918,677	0	—

- (1) We do not know when or in what amounts the selling stockholder may offer shares for sale. The selling stockholder might not sell any or all of the shares offered by this prospectus. Because the selling stockholder 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 stockholder 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 stockholder.
- (2) The address of Incyte Corporation is 1801 Augustine Cut-Off, Wilmington, DE 19803.

Relationship with Selling Stockholder

Collaboration Agreement

On January 8, 2018, we entered into a Target Discovery, Research Collaboration and Option Agreement, or collaboration agreement, with Incyte. Under the collaboration agreement, we will use our proprietary gene control platform to identify novel therapeutic targets with a focus on myeloproliferative neoplasms, and Incyte will receive options to obtain exclusive worldwide rights to intellectual property resulting from the collaboration for the development and commercialization of

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therapeutic products directed to up to seven validated targets. Incyte will have exclusive worldwide rights to develop and commercialize any therapies under the collaboration that modulate those validated targets.

Under the terms of the collaboration agreement, Incyte paid us \$10.0 million in up-front consideration, consisting of \$2.5 million in cash and \$7.5 million in prepaid research funding. Our activities under the collaboration agreement are subject to a joint research plan and, subject to certain exceptions, Incyte will be responsible for funding our activities under the research plan, including amounts in excess of the pre-paid research funding amount.

Should Incyte exercise all of its options under the agreement, we could receive up to \$54 million from Incyte in target selection and option exercise fees. For products resulting from the collaboration against each of the up to seven selected and validated targets, we could receive up to \$50 million in development and regulatory milestones, as well as up to \$65 million in commercial milestones. We would also be eligible to receive low single-digit royalties on sales of products resulting from the collaboration.

The term of collaboration agreement began on January 8, 2018 and, unless terminated by a party early, will continue until all royalty obligations for products arising from the collaboration expire. The collaboration agreement may be terminated by Incyte for convenience on sixty (60) days' prior written notice to us, or by us on thirty (30) days' written notice in the event Incyte or one of its affiliates or sublicensees challenges the validity or enforceability of certain patent rights controlled by us. The collaboration agreement may also be terminated by either of the parties on thirty (30) days' prior written notice in the event of an uncured material breach of the collaboration agreement by the other party or immediately in the case of certain bankruptcy events. Incyte's right to terminate for convenience and each party's right to terminate for uncured material breach may be exercised either with respect to the collaboration agreement in its entirety or, as applicable, in relation to the relevant validated target and associated therapeutic products.

The foregoing description of the material terms of the collaboration agreement is qualified in its entirety by the terms of the collaboration agreement, which we intend to file as an exhibit to our Annual Report on Form 10-K for the fiscal year ended December 31, 2017.

Stock Purchase Agreement

In addition, on January 8, 2018, we entered into a stock purchase agreement with Incyte, pursuant to which Incyte purchased 793,021 shares of our common stock for an aggregate purchase price of \$10.0 million in cash, or \$12.61 per share, in a private placement. The shares are subject to a lock-up restriction and a market stand-off agreement for a period of 12 months following the closing of the sale of the shares.

Pursuant to the terms of the stock purchase agreement, we agreed to file a registration statement covering the resale by Incyte of the shares within 20 days following the closing. We agreed to use commercially reasonable efforts to cause such registration statement to become effective no later than the last day of the fiscal quarter in which the shares are delivered to Incyte, and to keep such registration statement effective until the date the shares covered by such registration statement have been sold or may be sold without volume restrictions pursuant to Rule 144 under the Securities Act of 1933, as amended. We agreed to be responsible for all fees and expenses incurred in connection with the registration of the shares for resale. We granted to Incyte, and Incyte granted to us, customary indemnification rights in connection with the registration statement.

In addition, from the closing until the earlier of the second anniversary of the closing or the expiration or termination of the collaboration agreement, we have granted to Incyte the right to purchase up to its pro rata share of the securities offered in certain subsequent offerings of our

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common stock or common stock equivalents, subject to the terms and conditions set forth in the stock purchase agreement ("participation right"). On February 2, 2018, we closed an underwritten public offering of shares of our common stock (the "public offering") and, in connection therewith, Incyte exercised its participation right to undertake a side-by-side private placement at the same time as the public offering. On January 31, 2018, we entered into an amendment no. 1 to the stock purchase agreement to facilitate such private placement. Pursuant to the stock purchase agreement, as amended, Incyte purchased 125,656 shares of our common stock for an aggregate purchase price of \$1.2 million in cash, or \$9.55 per share, in a private placement. The closing of the sale of such shares took place concurrently with the closing of the public offering.

The foregoing descriptions of the terms and conditions of the stock purchase agreement and amendment no. 1 to the stock purchase agreement do not purport to be complete and are qualified in their entirety by reference to the full text of each such document, which are attached hereto as Exhibit 4.4 and Exhibit 4.5, respectively, and are incorporated by reference herein.

PLAN OF DISTRIBUTION

The shares covered by this prospectus may be offered and sold from time to time by the selling stockholder. The term "selling stockholder" includes donees, pledgees, transferees, assignees or other successors-in-interest selling shares received after the date of this prospectus from the selling stockholder as a gift, pledge, partnership distribution or other non-sale related transfer. The selling stockholder 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, market or trading facilities, 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, at fixed prices or in negotiated transactions. The selling stockholder may sell its 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 exchange distribution in accordance with the rules of the applicable exchange;
- in privately negotiated transactions;
- broker-dealers may agree with the selling stockholder to sell a specified number of such shares at a stipulated price per share;
- through the writing or settlement of options or other hedging transactions, whether through an options exchange or otherwise; or
- any other method permitted pursuant to applicable law.

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 stockholder 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 the selling stockholder. The selling stockholder may also sell the common stock short and redeliver the shares to close out such short positions. The selling stockholder 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 stockholder 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 stockholder may arrange for other broker-dealers to participate. Broker-dealers or agents may receive commissions, discounts or concessions from the selling stockholder in amounts to be negotiated immediately prior to the sale.

In offering the shares covered by this prospectus, the selling stockholder and any broker-dealers who execute sales for the selling stockholder may be deemed to be "underwriters" within the meaning

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of the Securities Act in connection with such sales. Any profits realized by the selling stockholder 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.

We have advised the selling stockholder 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 stockholder and their affiliates. In addition, we will make copies of this prospectus available to the selling stockholder for the purpose of satisfying the prospectus delivery requirements of the Securities Act. The selling stockholder 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 stockholder against certain liabilities, including certain liabilities under the Securities Act.

We have agreed with the selling stockholder 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 volume restrictions 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 Quarterly Report on Form 10-Q for the quarter ended June 30, 2017, filed with the SEC on August 9, 2017;
- (4) Our Quarterly Report on Form 10-Q for the quarter ended September 30, 2017, filed with the SEC on November 8, 2017;
- (5) 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, April 26, 2017, June 12, 2017, September 29, 2017, December 11, 2017, January 8, 2018 (except Item 7.01), January 12, 2018 and January 31, 2018;

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- (6) 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; and
- (7) Any other filings we make pursuant to the Exchange Act after the date of filing the registration statement of which this prospectus is a part 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.

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

918,677 Shares



Common Stock

PROSPECTUS

, 2018

PART II**INFORMATION NOT REQUIRED IN PROSPECTUS****Item 14. Other Expenses of Issuance and Distribution.**

Set forth below are estimates (except in the case of the SEC registration fee) of the amount of fees and expenses to be incurred in connection with the issuance and distribution of the offered securities, other than underwriting discounts and commissions.

SEC registration fee	\$ 1,086
Accounting fees and expenses	10,000
Legal fees and expenses	40,000
Miscellaneous fees and expenses	3,914
Total	<u>\$ 55,000</u>

Item 15. Indemnification of Directors and Officers.

Section 145 of the General Corporation Law of the State of Delaware ("DGCL") provides, generally, that a corporation shall have the power to indemnify any person who was or is a party or is threatened to be made a party to any threatened, pending or completed action, suit or proceeding (except actions by or in the right of the corporation) by reason of the fact that such person is or was a director, officer, employee or agent of the corporation against all expenses, judgments, fines and amounts paid in settlement actually and reasonably incurred by such person in connection with such action, suit or proceeding if such person acted in good faith and in a manner such person reasonably believed to be in or not opposed to the best interests of the corporation and, with respect to any criminal action or proceeding, had no reasonable cause to believe his or her conduct was unlawful. A corporation may similarly indemnify such person for expenses actually and reasonably incurred by such person in connection with the defense or settlement of any action or suit by or in the right of the corporation, *provided* that such person acted in good faith and in a manner he or she reasonably believed to be in or not opposed to the best interests of the corporation, and, in the case of claims, issues and matters as to which such person shall have been adjudged liable to the corporation, *provided* that a court shall have determined, upon application, that, despite the adjudication of liability but in view of all of the circumstances of the case, such person is fairly and reasonably entitled to indemnity for such expenses which such court shall deem proper.

Section 102(b)(7) of the DGCL provides, generally, that our certificate of incorporation may contain a provision eliminating or limiting the personal liability of a director to the corporation or its shareholders for monetary damages for breach of fiduciary duty as a director, *provided* that such provision may not eliminate or limit the liability of a director (i) for any breach of the director's duty of loyalty to the corporation or its shareholders, (ii) for acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law, (iii) under section 174 of the DGCL, or (iv) for any transaction from which the director derived an improper personal benefit. No such provision may eliminate or limit the liability of a director for any act or omission occurring prior to the date when such provision became effective.

Our restated certificate of incorporation provides that we will indemnify each person who was or is a party or threatened to be made a party to or is involved in any threatened, pending or completed action, suit or proceeding, whether civil, criminal, administrative or investigative (other than an action by or in the right of us) by reason of the fact that he or she is or was, or has agreed to become, our director or officer, or is or was serving, or has agreed to serve, at our request as a director, officer, partner, employee or trustee of, or in a similar capacity with, another corporation, partnership, joint venture, trust or other enterprise (all such persons being referred to as an "Indemnitee"), or by reason

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of any action alleged to have been taken or omitted in such capacity, against all expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred in connection with such action, suit or proceeding and any appeal therefrom, if such Indemnitee acted in good faith and in a manner he or she reasonably believed to be in, or not opposed to, our best interests, and, with respect to any criminal action or proceeding, he or she had no reasonable cause to believe his or her conduct was unlawful. Our restated certificate of incorporation also provides that we will indemnify any Indemnitee who was or is a party to an action or suit by or in the right of us to procure a judgment in our favor by reason of the fact that the Indemnitee is or was, or has agreed to become, our director or officer, or is or was serving, or has agreed to serve, at our request as a director, officer, partner, employee or trustee of, or in a similar capacity with, another corporation, partnership, joint venture, trust or other enterprise, or by reason of any action alleged to have been taken or omitted in such capacity, against all expenses (including attorneys' fees) and, to the extent permitted by law, amounts paid in settlement actually and reasonably incurred in connection with such action, suit or proceeding, and any appeal therefrom, if the Indemnitee acted in good faith and in a manner he or she reasonably believed to be in, or not opposed to, our best interests, except that no indemnification shall be made with respect to any claim, issue or matter as to which such person shall have been adjudged to be liable to us, unless a court determines that, despite such adjudication but in view of all of the circumstances, he or she is entitled to indemnification of such expenses. Notwithstanding the foregoing, to the extent that any Indemnitee has been successful, on the merits or otherwise, he or she will be indemnified by us against all expenses (including attorneys' fees) actually and reasonably incurred by him or her or on his or her behalf in connection therewith. If we do not assume the defense, expenses must be advanced to an Indemnitee under certain circumstances.

We have entered into indemnification agreements with our directors and executive officers. In general, these agreements provide that we will indemnify the director or executive officer to the fullest extent permitted by law for claims arising in his or her capacity as a director or officer of our company or in connection with their service at our request for another corporation or entity. The indemnification agreements also provide for procedures that will apply in the event that a director or executive officer makes a claim for indemnification and establish certain presumptions that are favorable to the director or executive officer.

We maintain a general liability insurance policy that covers certain liabilities of our directors and officers arising out of claims based on acts or omissions in their capacities as directors or officers.

Certain of our non-employee directors may, through their relationships with their employers, be insured and/or indemnified against certain liabilities in their capacity as members of our board of directors.

The underwriting agreement we entered into in connection with the initial public offering of our common stock provides that the underwriters will indemnify, under certain conditions, our directors and officers (as well as certain other persons) against certain liabilities arising in connection with such offering.

Insofar as the forgoing provisions permit indemnification of directors, executive officers, or persons controlling us for liability arising under the Securities Act of 1933, as amended, or the Securities Act, we have been informed that, in the opinion of the Securities and Exchange Commission, such indemnification is against public policy as expressed in the Securities Act and is therefore unenforceable.

Item 16. Exhibits

<u>Exhibit No.</u>	<u>Description</u>
4.1	Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K filed with the SEC on July 6, 2016 (File No. 001-37813))
4.2	Amended and Restated By-laws of the Registrant (incorporated by reference to Exhibit 3.2 to the Registrant's Current Report on Form 8-K filed with the SEC on July 6, 2016 (File No. 001-37813))
4.3	Second Amended and Restated Investors' Rights Agreement dated October 9, 2014, as amended, among the Registrant and the other parties thereto (incorporated by reference to Exhibit 4.2 to the Registrant's Registration Statement on Form S-1 filed with the SEC on June 3, 2016 (File No. 333-211818))
4.4*	Stock Purchase Agreement, dated January 8, 2018, among the Registrant and Incyte Corporation
4.5	Amendment No. 1 to Stock Purchase Agreement, dated January 31, 2018, among the Registrant and Incyte Corporation
5.1	Opinion of Wilmer Cutler Pickering Hale and Dorr LLP
23.1	Consent of Ernst & Young LLP, independent registered public accounting firm
23.2	Consent of Wilmer Cutler Pickering Hale and Dorr LLP (included in Exhibit 5.1)
24.1*	Powers of Attorney (included in the signature pages to the Registrant's Registration Statement)

* Previously filed.

Item 17. Undertakings.

The undersigned Registrant hereby undertakes:

- (a) (1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement:
 - (i) to include any prospectus required by Section 10(a)(3) of the Securities Act of 1933, as amended (the "Securities Act");
 - (ii) to reflect in the prospectus any facts or events arising after the effective date of this registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in this registration statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the Commission pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than a 20 percent change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective registration statement; and

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- (iii) to include any material information with respect to the plan of distribution not previously disclosed in this registration statement or any material change to such information in this registration statement;

provided, however, that paragraphs (a)(1)(i), (a)(1)(ii) and (a)(1)(iii) do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the Commission by the Registrant pursuant to Section 13 or Section 15(d) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), that are incorporated by reference in this registration statement, or is contained in a form of prospectus filed pursuant to Rule 424(b) that is part of this registration statement.

- (2) That, for the purposes of determining any liability under the Securities Act, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at the time shall be deemed to be the initial *bona fide* offering thereof.
- (3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.
- (4) That, for the purpose of determining liability under the Securities Act to any purchaser:
 - (i) each prospectus filed by the Registrant pursuant to Rule 424(b)(3) shall be deemed to be part of the registration statement as of the date the filed prospectus was deemed part of and included in the registration statement; and
 - (ii) each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5), or (b)(7) as part of a registration statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vii) or (x) for the purpose of providing the information required by Section 10(a) of the Securities Act of 1933 shall be deemed to be part of and included in the registration statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in the prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a new effective date of the registration statement relating to the securities in the registration statement to which that prospectus relates, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof; *provided, however*, that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such effective date.
- (b) The undersigned Registrant hereby undertakes that, for purposes of determining any liability under the Securities Act, each filing of the Registrant's annual report pursuant to Section 13(a) or 15(d) of the Exchange Act (and, where applicable, each filing of an employee benefit plan's annual report pursuant to Section 15(d) of the Exchange Act) that is incorporated by reference in this registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.
- (c) Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the Registrant pursuant to the indemnification provisions described herein, or otherwise, the Registrant has been advised that in the opinion of the Commission

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such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the Registrant of expenses incurred or paid by a director, officer or controlling person of the Registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the Registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, as amended, the Registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this Pre-Effective Amendment No. 1 to the Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Cambridge, Commonwealth of Massachusetts, on February 2, 2018.

SYROS PHARMACEUTICALS, INC.

By: /s/ NANCY SIMONIAN

Name: Nancy Simonian, M.D.
Title: *President, Chief Executive Officer and Director*

Pursuant to the requirements of the Securities Act of 1933, as amended, this Pre-Effective Amendment No. 1 to the Registration Statement has been signed by the following persons in the capacities and on the dates indicated.

<u>Signature</u>	<u>Title</u>	<u>Date</u>
<hr/> /s/ NANCY SIMONIAN Nancy Simonian, M.D.	President, Chief Executive Officer and Director (principal executive officer and principal financial officer)	February 2, 2018
<hr/> /s/ COLLEEN DESIMONE Colleen DeSimone	Vice President, Finance (principal accounting officer)	February 2, 2018
<hr/> * Srinivas Akkaraju, M.D., Ph.D.	Director	February 2, 2018
<hr/> * Marsha H. Fanucci	Director	February 2, 2018
<hr/> * Amir Nashat, Ph.D.	Director	February 2, 2018
<hr/> * Robert T. Nelsen	Director	February 2, 2018
<hr/> * Sanj K. Patel	Director	February 2, 2018

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<u>Signature</u>	<u>Title</u>	<u>Date</u>
* _____ Vicki L. Sato, Ph.D.	Director	February 2, 2018
* _____ Phillip A. Sharp, Ph.D.	Director	February 2, 2018
* _____ Peter Wirth	Director	February 2, 2018
* _____ Richard A. Young, Ph.D.	Director	February 2, 2018
*By: _____ /s/ GERALD QUIRK Gerald Quirk <i>Attorney-in-Fact</i>		

AMENDMENT NO. 1 TO STOCK PURCHASE AGREEMENT

This Amendment No. 1 to Stock Purchase Agreement (this "Amendment") is dated as of January 31, 2018 (the "Amendment Date"), between Syros Pharmaceuticals, Inc., a Delaware corporation (the "Company"), and Incyte Corporation, a Delaware corporation ("Purchaser"), to amend that certain Stock Purchase Agreement, dated as of January 8, 2018, between the Company and Purchaser (the "Agreement"). Capitalized terms used and not otherwise defined herein shall have the meanings ascribed to such terms in the Agreement.

WHEREAS, in Section 5.8 of the Agreement, the Company granted to Purchaser the right to purchase up to Purchaser's Pro-Rata Share in the event of a Subsequent Financing;

WHEREAS, the Company intends to undertake a Public Offering, subject to market and other conditions (the "2018 Public Offering"); and

WHEREAS, Purchaser, pursuant to the terms and conditions of the Agreement (as amended by this Amendment), desires to undertake a side-by-side private placement at the same time as the 2018 Public Offering, in an amount equal to Purchaser's Pro-Rata Share and at a price per share equal to the public offering price per share that the Common Stock is sold to the public in the 2018 Public Offering (the "Public Offering Price").

NOW, THEREFORE, IN CONSIDERATION of the mutual covenants contained herein, and for other good and valuable consideration the receipt and adequacy of which are hereby acknowledged, the Company and Purchaser agree as follows:

1. Amendment of Section 2.1. Section 2.1 of the Agreement is hereby deleted in its entirety and the following is inserted in lieu thereof:

"Subject to the terms and conditions of this Agreement, the Company agrees to sell to Purchaser at the Initial Closing, free and clear of all Liens, and Purchaser agrees to purchase from the Company at the Initial Closing, 793,021 shares of Common Stock (the "Initial Shares") at a price per share of \$12.61 for an aggregate purchase price of \$9,999,994.81 (the "Initial Purchase Price"). Subject to the satisfaction or waiver of the conditions set forth in Section 2.4, the Initial Closing shall take place remotely via the exchange of documents and signatures at 10:00 a.m. Eastern Time on January 8, 2018, or at such other time and location as the Company and Purchaser shall mutually agree (which time and location are designated as the "Initial Closing" and the date thereof as the "Initial Closing Date"). Subject to the terms and conditions of this Agreement, the Company agrees to sell to Purchaser at the Additional Closing, free and clear of all Liens, and Purchaser agrees to purchase from the Company at the Additional Closing, 125,656 shares of Common Stock ("Additional Shares") at a price per share of \$9.55 for an aggregate purchase price of \$1,200,014.80 (the "Additional Purchase Price"). Upon satisfaction or waiver of the conditions set forth in Section 2.4, the Additional Closing shall take place remotely via the exchange of documents and signatures concurrently with the closing of the 2018 Public Offering, which the Company and Purchaser anticipate will be on or about two (2) Business Days following the Amendment Date, or at such other time and location as the Company and Purchaser shall mutually agree (which time

and location are designated as the "Additional Closing" and the date thereof as the "Additional Closing Date"). The shares of Common Stock issued to Purchaser pursuant to this Agreement (including the Initial Shares and any Additional Shares) shall be referred to in this Agreement as the "Shares," unless otherwise specified. Similarly, in the event there is more than one closing, the term "Closing" shall apply to each such closing, as applicable; the term "Closing Date" shall apply to the date of each such closing, as applicable; and the term "Purchase Price" shall apply to the Initial Purchase Price or the Additional Purchase Price, as applicable, in each case, unless otherwise specified."

2. Amendment of Section 2.4. Section 2.4 of the Agreement is hereby amended by:

(a) Deleting the phrase "the date hereof" where it appears therein and inserting in lieu thereof "the date hereof, as of the Amendment Date and as of each Closing Date."

(b) Inserting the following as new Section 2.4(a)(v) and new Section 2.4(b)(x):

"Solely with respect to the Additional Closing, any of J.P. Morgan Securities LLC, Cowen and Company, LLC or Piper Jaffray & Co., the representatives of the several underwriters for the 2018 Public Offering (the "Underwriters"), shall have purchased, concurrent with the purchase of the Additional Shares by Purchaser hereunder, the Underwritten Shares (as defined in the Underwriting Agreement to effect the 2018 Public Offering (the "Underwriting Agreement")) at the Public Offering Price (less any underwriting discounts or commissions)."

3. Amendment of Sections 3.1 and 3.2. The first sentence of each of Sections 3.1 and 3.2 of the Agreement is hereby amended by deleting the phrase "the date hereof" where it appears therein and inserting in lieu thereof "the date hereof and as of the Amendment Date."

4. Amendment of Section 3.1(a). The second sentence of Section 3.1(a) of the Agreement is hereby deleted in its entirety and the following is inserted in lieu thereof:

"The Company has not issued any capital stock since its most recently filed periodic report under the Exchange Act, other than

pursuant to this Agreement and the 2018 Public Offering, pursuant to the exercise of stock options under the Company's stock incentive plans and the issuance of shares of Common Stock pursuant to the Company's at-the-market sales agreement."

5. Amendment of Section 5.1. Section 5.1 of the Agreement is hereby deleted in its entirety and the following is inserted in lieu thereof:

"5.1 Stock Ownership Governance.

(a) Lock-Up Period. Excluding any transfers of Initial Shares between Purchaser and any of its Affiliates, during the twelve (12) month period beginning on the Initial Closing Date and ending on the first anniversary thereof (the "Lock-Up Period"), Purchaser shall not, and shall not cause any other holder of the Initial Shares to, without the prior written consent of the Company, sell, contract to sell, pledge or otherwise

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dispose of, directly or indirectly, any Initial Shares or enter into a transaction which would have the same effect. The Purchaser acknowledges that the Company shall impose stop-transfer instructions with respect to the Initial Shares until the end of the Lock-Up Period in accordance with the transfer restrictions set forth in this Section 5.1(a).

(b) Market Stand-Off Agreement. During the Lock-Up Period, Purchaser agrees that in connection with any registration of the Company's securities that, upon the request of the Company or the underwriters managing any underwritten offering of the Company's securities, Purchaser will not sell, make any short sale of, loan, grant any option for the purchase of, or otherwise dispose of any Initial Shares without the prior written consent of the Company or such underwriters, as the case may be, for such period of time within the Lock-Up Period from the effective date of such registration as the Company or the underwriters may specify.

(c) Remedies. Without prejudice to the rights and remedies otherwise available to the parties, the Company shall be entitled to equitable relief by way of injunction if Purchaser or any other holder of the Initial Shares breaches or threatens to breach any of the provisions of this Section 5.1."

6. Amendment of Section 5.7(a). Clause (iv) of Section 5.7(a) of the Agreement is hereby deleted in its entirety and the following is inserted in lieu thereof: "(iv) following the expiration of the Lock-Up Period (solely as to the Initial Shares);"

7. Amendment of Section 5.8(a). The first sentence of Section 5.8(a) of the Agreement is hereby amended by deleting the phrase "Closing Date" where it appears therein and inserting in lieu thereof "Initial Closing Date."

8. Underwriters Exercise of Overallotment.

8.1 Purchase and Sale of Option Shares: Option Closings. In the event that the Underwriters exercise, in full or in part, their right under the Underwriting Agreement to purchase additional shares of Common Stock to cover overallotments, if any, the Company shall provide written notice to Purchaser of such exercise in accordance with Section 5.8 of the Agreement (as amended by this Amendment). In the event that Purchaser elects, pursuant to Section 5.8 of the Agreement (as amended by this Amendment), to purchase its Pro-Rata Share of shares of Common Stock in relation to any such exercise ("Option Shares"), subject to the terms and conditions of the Agreement (as amended by this Amendment), the Company shall sell to Purchaser at an Option Closing (as defined below), free and clear of all Liens, and Purchaser agrees to purchase from the Company at such Option Closing, the applicable Option Shares at a price per share of \$9.55 for an aggregate purchase price equal to the price per share multiplied by the number of Option Shares purchased in such Option Closing (for each Option Closing, if any, the "Option Purchase Price"). Upon satisfaction or waiver of the conditions set forth in Section 2.4 of the Agreement (as amended by this Amendment), any Option Closing shall take place remotely via the exchange of documents and signatures concurrently with the closing of the Underwriters' purchase of shares of Common Stock upon exercise of their overallotment option, or at such other time and location as the Company and Purchaser shall mutually agree (each such

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time and location are designated as an "Option Closing" and the date thereof as an "Option Closing Date").

8.2. Amendment of Section 2.1 for an Option Closing. In the event of an Option Closing, the last two sentences of Section 2.1 of the Agreement (as amended herein) shall be deleted in their entirety and the following inserted in lieu thereof:

"The shares of Common Stock issued to Purchaser pursuant to this Agreement (including the Initial Shares, the Additional Shares and any Option Shares) shall be referred to in this Agreement as the "Shares," unless otherwise specified. Similarly, in the event there is more than one closing, the term "Closing" shall apply to each such closing, as applicable; the term "Closing Date" shall apply to the date of each such closing, as applicable; and the term "Purchase Price" shall apply to the Initial Purchase Price, the Additional Purchase Price or an Option Purchase Price, as applicable, in each case, unless otherwise specified."

8.3. Amendment of Section 2.4 for an Option Closing. In the event of an Option Closing, Section 2.4 of the Agreement shall be amended by inserting the following as new Section 2.4(a)(vi) and new Section 2.4(b)(xi):

"Solely with respect to an Option Closing, the Underwriters shall have purchased, concurrent with the purchase of the Option

Shares by Purchaser hereunder, the Option Shares (for purposes of this clause, as defined in the Underwriting Agreement) at the Public Offering Price (less any underwriting discounts or commissions).”

9. Termination of Amendment. This Amendment and the obligations, representations and warranties of the parties under the Agreement (as amended by this Amendment) with respect to the purchase of Additional Shares shall automatically terminate and be of no further force and effect upon the earliest to occur, if any, of: (a) either the Company, on the one hand, or the Underwriters, on the other hand, advising the other in writing, prior to the execution of the Underwriting Agreement, that they have determined not to proceed with the 2018 Public Offering, (b) termination of the Underwriting Agreement (other than the provisions thereof which survive termination) prior to the sale of any of the Common Stock to the Underwriters, or (c) the Underwriting Agreement has not become effective by March 31, 2018.

10. Entire Agreement. The Agreement, as supplemented and modified by this Amendment, together with the exhibits and schedules thereto, contains the entire understanding of the parties with respect to the subject matter hereof and supersedes all prior agreements and understandings, oral or written, with respect to such matters, which the parties acknowledge have been merged into the Agreement.

11. Governing Law. This Amendment shall in all respects be governed by and construed in accordance with the laws of the State of Delaware, USA, including all matters of construction, validity and performance, in each case without reference to any conflict of law rules that might lead to the application of the laws of any other jurisdiction.

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12. Execution in Counterparts. This Amendment may be executed in two or more counterparts, all of which when taken together shall be considered one and the same agreement and shall become effective when counterparts have been signed by each party and delivered to each other party, it being understood that the parties need not sign the same counterpart. In the event that any signature is delivered by facsimile transmission or by e-mail delivery of a “.pdf” format data file, such signature shall create a valid and binding obligation of the party executing (or on whose behalf such signature is executed) with the same force and effect as if such facsimile or “.pdf” signature page were an original thereof.

13. Remaining Provisions of the Agreement. Except as provided herein, each of the other provisions of the Agreement shall remain in full force and effect.

14. References. Upon the effectiveness of this Amendment, on and after the date hereof, each reference in the Agreement to “this Agreement,” “hereunder,” “hereof,” “herein” or words of like import shall mean and be a reference to the Agreement, as amended hereby.

(Signature Pages Follow)

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IN WITNESS WHEREOF, the parties hereto have caused this Amendment No. 1 to Stock Purchase Agreement to be duly executed by their respective authorized signatories as of the date first indicated above.

SYROS PHARMACEUTICALS, INC.

By: /s/ Nancy Simonian
Name: Nancy Simonian, M.D.
Title: Chief Executive Officer

INCYTE CORPORATION

By: /s/ Hervé Hoppenot
Name: Hervé Hoppenot
Title: President and Chief Executive Officer

[Signature Page to Amendment No. 1 to Stock Purchase Agreement]

WILMERHALE

+1 617 526 6000 (t)

+1 617 526 5000 (f)

wilmerhale.com

February 2, 2018

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

Registration Statement on Form S-3

Ladies and Gentlemen:

This opinion is furnished to you in connection with a Registration Statement on Form S-3 (the "Registration Statement") filed with the Securities and Exchange Commission (the "Commission") under the Securities Act of 1933, as amended (the "Securities Act"), for the registration of the resale of an aggregate of 918,677 shares (the "Shares") of common stock, \$0.001 par value per share (the "Common Stock"), of Syros Pharmaceuticals, Inc., a Delaware corporation (the "Company"). All of the Shares are being registered on behalf of certain stockholders of the Company (the "Selling Stockholder").

We are acting as counsel for the Company in connection with the registration for resale of the Shares. We have examined signed copies of the Registration Statement as filed with the Commission. We have also examined and relied upon minutes of meetings of the stockholders and the Board of Directors of the Company as provided to us by the Company, the Certificate of Incorporation and By-Laws of the Company, each as restated and/or amended to date, and such other documents as we have deemed necessary for purposes of rendering the opinions hereinafter set forth.

In our examination of the foregoing documents, we have assumed the genuineness of all signatures, the authenticity of all documents submitted to us as originals, the conformity to original documents of all documents submitted to us as copies, the authenticity of the originals of such latter documents and the legal competence of all signatories to such documents.

Our opinion below, insofar as it relates to the Shares being fully paid, is based solely on a certificate of the Chief Executive Officer of the Company confirming the Company's receipt of the consideration called for by the applicable resolutions authorizing the issuance of such Shares.

We assume that the appropriate action will be taken, prior to the offer and sale of the Shares by the Selling Stockholder, to register and qualify the Shares for sale under all applicable state securities or "blue sky" laws.

Wilmer Cutler Pickering Hale and Dorr LLP, 60 State Street, Boston, Massachusetts 02109

Beijing Berlin Boston Brussels Denver Frankfurt London Los Angeles New York Palo Alto Washington

We express no opinion herein as to the laws of any state or jurisdiction other than the state laws of the Commonwealth of Massachusetts, the General Corporation Law of the State of Delaware and the federal laws of the United States of America.

Based upon and subject to the foregoing, we are of the opinion that the Shares have been duly authorized for issuance and are validly issued, fully paid and nonassessable.

It is understood that this opinion is to be used only in connection with the offer and sale of the Shares while the Registration Statement is in effect.

Please note that we are opining only as to the matters expressly set forth herein, and no opinion should be inferred as to any other matters. This opinion is based upon currently existing statutes, rules, regulations and judicial decisions, and we disclaim any obligation to advise you of any change in any of these sources of law or subsequent legal or factual developments which might affect any matters or opinions set forth herein.

We hereby consent to the filing of this opinion with the Commission as an exhibit to the Registration Statement in accordance with the requirements of Item 601(b)(5) of Regulation S-K under the Securities Act and to the use of our name therein and in the related Prospectus under the caption "Legal Matters." In giving such consent, we do not hereby admit that we are in the category of persons whose consent is required under Section 7 of the Securities Act or the rules and regulations of the Commission.

Very truly yours,

WILMER CUTLER PICKERING

HALE AND DORR LLP

By: /s/ Cynthia Mazareas
Cynthia Mazareas, a Partner

Consent of Independent Registered Public Accounting Firm

We consent to the reference to our firm under the caption "Experts" in the Registration Statement on Form S-3 and related Prospectus of Syros Pharmaceuticals, Inc. for the registration of 918,677 shares of its common stock and to the incorporation by reference therein of our report dated March 20, 2017, with respect to the consolidated financial statements of Syros Pharmaceuticals, Inc., included in its Annual Report on Form 10-K for the year ended December 31, 2016, filed with the Securities and Exchange Commission.

/s/ Ernst & Young LLP

Boston, Massachusetts
February 2, 2018
