

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

**FORM S-3  
REGISTRATION STATEMENT  
UNDER  
THE SECURITIES ACT OF 1933**

**SYROS PHARMACEUTICALS, INC.**

(Exact Name of Registrant as Specified in Its Charter)

Delaware  
(State or Other Jurisdiction of  
Incorporation or Organization)

45-3772460  
(I.R.S. Employer  
Identification Number)

35 CambridgePark Drive, 4th Floor  
Cambridge, Massachusetts 02140  
(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.  
35 CambridgePark Drive, 4th Floor  
Cambridge, Massachusetts 02140  
(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  
Syros Pharmaceuticals, Inc.  
35 CambridgePark Drive, 4th Floor  
Cambridge, Massachusetts 02140  
Telephone: (617) 744-1340

Cynthia T. Mazareas  
Wilmer Cutler Pickering Hale and Dorr LLP  
60 State Street  
Boston, Massachusetts 02109  
Telephone: (617) 526-6000  
Fax: (617) 526-5000

**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  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	14,140,625	\$10.45	\$147,769,531.25	\$16,121.66

- (1) The shares of common stock will be offered for resale by the selling stockholders pursuant to the prospectus contained herein. 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.
- (2) This registration statement registers the resale of (i) 10,312,500 outstanding shares of common stock of the Registrant, (ii) 1,000,000 shares of common stock of the Registrant issuable upon the exercise of pre-funded warrants issued by the Registrant at an exercise price of \$0.01 per share, and (iii) 2,828,125 shares of common stock of the Registrant issuable upon the exercise of warrants issued by the Registrant (or issuable upon exercise of pre-funded warrants to purchase shares of the Registrant's common stock that are issuable to holders of warrants upon exercise of such warrants for pre-funded warrants in lieu of common stock) at an exercise price of \$11.00 per share, or if exercised for a pre-funded warrant in lieu thereof, \$10.99 per pre-funded warrant (representing the warrant exercise price of \$11.00 per share minus the \$0.01 per share exercise price of each such pre-funded warrant).
- (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 5, 2021.

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 stockholders 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 stockholders named in this prospectus are 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 January 7, 2021**

**PROSPECTUS**

**14,140,625 Shares**



**Common Stock**

This prospectus relates to the resale from time to time of up to 14,140,625 shares of common stock of Syros Pharmaceuticals, Inc. by the selling stockholders listed on page 7, including their pledgees, assignees, donees, transferees or their respective successors-in-interest, which consist of 10,312,500 outstanding shares of our common stock held by the selling stockholders, 1,000,000 shares of our common stock issuable upon the exercise of outstanding pre-funded warrants held by the selling stockholders to purchase shares of our common stock and 2,828,125 shares of our common stock issuable upon the exercise of outstanding warrants held by the selling stockholders to purchase shares of our common stock (the “Warrants”) (or issuable upon exercise of pre-funded warrants to purchase shares of our common stock that are issuable to holders of Warrants upon exercise of such Warrants for pre-funded warrants in lieu of common stock). We will not receive any proceeds from the sale of the shares offered by this prospectus.

We have agreed, pursuant to a registration rights agreement that we have entered into with the selling stockholders, to bear all of the expenses incurred in connection with the registration of these shares. The selling stockholders will pay or assume discounts, commissions, fees of underwriters, selling brokers or dealer managers and similar expenses, if any, incurred for the sale of these shares of our common stock.

The selling stockholders identified in this prospectus, or their pledgees, assignees, donees, transferees or their respective 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. For a list of the selling stockholders, see the section entitled “Selling Stockholders” on page 7.

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 traded on the Nasdaq Global Select Market (“Nasdaq”) under the symbol “SYRS.” On January 6, 2021, the last reported closing sale price of our common stock on Nasdaq was \$10.32 per share. You are urged to obtain current market quotations for our 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.”

**Investing in our common stock involves a high degree of risk. See “[Risk Factors](#)” beginning on page 3 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 adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.**

**The date of this prospectus is \_\_\_\_\_, 2021.**

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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 seeking to redefine the power of small molecules to control the expression of genes. Based on our unique ability to elucidate regulatory regions of the genome, we aim to develop medicines that provide a profound benefit for patients with diseases that have eluded other genomics-based approaches. We are currently focused on developing treatments for cancer and diseases resulting from mutations of a single gene, also known as monogenic diseases, and building a pipeline of gene control medicines.

### 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 35 CambridgePark Drive, 4<sup>th</sup> Floor, Cambridge, Massachusetts 02140, and our telephone number is (617) 744-1340. Our website address is [www.syros.com](http://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 subsidiaries, Syros Securities Corporation, a Massachusetts corporation, and Syros Pharmaceuticals (Ireland) Limited, an Irish limited liability company.

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 (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	14,140,625 shares, consisting of 10,312,500 outstanding shares of our common stock, 1,000,000 shares of our common stock issuable upon the exercise of outstanding pre-funded warrants and 2,828,125 shares of our common stock issuable upon the exercise of Warrants (or issuable upon exercise of pre-funded warrants to purchase shares of our common stock that are issuable to holders of Warrants upon exercise of such Warrants for pre-funded warrants in lieu of common stock).
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 3 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 (“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 and expand clinical trials of our product candidates and our expectations for the timing, quantity and quality of information to be reported from our clinical trials of SY-1425, SY-2101 and SY-5609;
- 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 ability to discover and develop compounds suitable for clinical development and the timing for designation of future development candidates;
- our ability to replicate in any clinical trial of one of our product candidates the results we observed in preclinical or earlier clinical studies of such product candidate;
- our plans to research, develop, seek approval for, manufacture and commercialize our current and future product candidates;
- our plans to develop and seek approval of companion diagnostic tests for use in identifying patients who may benefit from treatment with our products and product candidates;
- our expectations regarding the potential benefits of our gene control platform and our approach;
- our ability to enter into, and the terms and timing of, any collaborations, license agreements, or other arrangements;
- whether a drug candidate will be nominated to enter investigational new drug application-enabling studies under our sickle cell disease collaboration with Global Blood Therapeutics, Inc. (“GBT”), whether GBT will exercise its option to exclusively license intellectual property arising from the collaboration, whether and when any option exercise fees, milestone payments or royalties under the collaboration agreement with GBT will ever be paid, and whether we exercise our U.S. co-promotion option under the GBT agreement;
- whether our target discovery collaboration with Incyte Corporation (“Incyte”), will yield any validated targets, whether Incyte will exercise any of its options to exclusively license intellectual property directed to such targets, and whether and when any of the target validation fees, option exercise fees, milestone payments or royalties under the Incyte collaboration will ever be paid;
- the potential benefits of any future collaboration;
- developments relating to our competitors and our industry;
- the impact of government laws and regulations;
- the timing of and our ability to file new drug applications and 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 and cash equivalents 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; 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. In particular, the extent to which the COVID-19 outbreak continues to impact our operations and those of the third parties on which we rely will depend on future developments, which are highly uncertain and cannot be predicted with confidence, including the duration and severity of the outbreak, additional or modified government actions, and the actions that may be required to contain the virus or treat its impact. COVID-19 has and may continue to adversely impact our operations and workforce, including our discovery research, supply chain and clinical trial operations activities, which in turn could have an adverse impact on our business and financial results. Our forward - looking statements also 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 forms a part to permit the 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 or other disposition of shares of our common stock held 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 these 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 STOCKHOLDERS

On December 4, 2020, we entered into a securities purchase agreement (the “Purchase Agreement”) with certain institutional and accredited investors (the “Investors”), pursuant to which we issued and sold in a private placement (the “Private Placement”) an aggregate of 10,312,500 shares of our common stock and, in lieu of shares of common stock, pre-funded warrants to purchase an aggregate of 1,000,000 shares of our common stock, and accompanying Warrants to purchase an aggregate of up to 2,828,125 additional shares of common stock (or pre-funded warrants to purchase common stock in lieu thereof) at a price of \$8.00 per unit, consisting of a share of our common stock and an accompanying Warrant to purchase 0.25 shares of our common stock (a “Common Stock Unit”), or \$7.99 per unit, consisting of a pre-funded warrant to purchase a share of our common stock and an accompanying Warrant to purchase 0.25 shares of our common stock (a “Pre-Funded Warrant Unit”). The price per Pre-Funded Warrant Unit represents the price of \$8.00 per Common Stock Unit sold in the Private Placement, minus the \$0.01 per share exercise price of each pre-funded warrant included in a Pre-Funded Warrant Unit. The exercise price of the Warrants is \$11.00 per share, or if exercised for a pre-funded warrant in lieu thereof, \$10.99 per pre-funded warrant (representing the Warrant exercise price of \$11.00 per share minus the \$0.01 per share exercise price of each such pre-funded warrant). The closing of the issuance and sale of these securities was consummated on December 8, 2020 (the “Private Placement Closing Date”). The Warrants are exercisable at any time during the period beginning on June 8, 2021 and ending on December 8, 2025. The pre-funded warrants are exercisable at any time after their original issuance and will not expire. The shares issuable upon exercise of the Warrants and pre-funded warrants will become eligible for sale by the selling stockholders under this prospectus only when the Warrants or pre-funded warrants are exercised. We cannot predict when or whether any of the selling stockholders will exercise their Warrants or pre-funded warrants.

The Warrants and pre-funded warrants issued or issuable in the Private Placement provide that a holder of Warrants or pre-funded warrants does not have the right to exercise any portion of its Warrants or pre-funded warrants if such holder, together with its affiliates, would beneficially own in excess of 9.99% of the number of shares of our common stock outstanding immediately after giving effect to such exercise (the “Beneficial Ownership Limitation”); provided, however, that each holder may increase or decrease the Beneficial Ownership Limitation by giving notice to the Company, but not to any percentage in excess of 19.99%.

In connection with the Private Placement, we entered into a registration rights agreement with the Investors, dated as of December 4, 2020 (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 and the shares of common stock underlying the Warrants and pre-funded warrants described above. We agreed to file such registration statement within 30 days following the Private Placement Closing Date. The Registration Rights Agreement includes customary indemnification rights in connection with the registration statement. The registration statement of which this prospectus forms a part has been filed in accordance with the Registration Rights Agreement.

We received gross proceeds of approximately \$90.5 million from the Private Placement, before deducting offering expenses, and excluding any proceeds that we may receive upon exercise of any pre-funded warrants and Warrants.

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 are filed as exhibits to the registration statement of which this prospectus forms a part, and are incorporated by reference herein.

This prospectus covers the sale or other disposition by the selling stockholders of up to the total number of shares of our common stock that were issued to the Investors pursuant to the Purchase Agreement, plus the total number of shares of our common stock issuable upon exercise of the Warrants and pre-funded warrants issued or

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issuable to the selling stockholders, without giving effect to the Beneficial Ownership Limitation described above. 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 January 3, 2021. The information in the table below with respect to the selling stockholders has been obtained from the respective selling stockholders. When we refer to the “selling stockholders” in this prospectus, or, if required, a post-effective amendment to the registration statement of which this prospectus is a part, we mean the selling stockholders listed in the table below as offering shares, as well as their respective pledgees, assignees, donees, transferees or successors-in-interest. Throughout this prospectus, when we refer to the shares of our common stock being registered on behalf of the selling stockholders, we are referring to the shares of our common stock and the shares underlying the Warrants and pre-funded warrants issued or issuable to the selling stockholders pursuant to the Purchase Agreement, without giving effect to the Beneficial Ownership Limitation described above. The selling stockholders may sell all, some or none of the shares of common stock subject to this prospectus. See “Plan of Distribution” below as it may be supplemented and amended from time to time.

The number of shares of common stock beneficially owned prior to the offering for each selling stockholder includes all shares of our common stock beneficially held by such selling stockholder as of January 3, 2021, which includes (i) all shares of our common stock purchased by such selling stockholder in the Private Placement and (ii) all shares of common stock issuable upon exercise of the pre-funded warrants purchased by such selling stockholder in the Private Placement. The percentages of shares owned before and after the offering are based on 56,197,104 shares of common stock outstanding as of January 3, 2021, which includes the outstanding shares of common stock offered by this prospectus but does not include any shares of common stock offered by this prospectus that are issuable pursuant to warrants and are deemed outstanding in the table below because they are beneficially owned by a person.

Beneficial ownership is determined in accordance with the rules of the SEC and includes voting or investment power with respect to our common stock. Generally, a person “beneficially owns” shares of our common stock if the person has or shares with others the right to vote those shares or to dispose of them, or if the person has the right to acquire voting or disposition rights within 60 days. In computing the number of shares of our common stock beneficially owned by a person and the percentage ownership of that person, we deemed outstanding shares of common stock issuable upon the exercise of pre-funded warrants held by that selling stockholder described above because all are exercisable within 60 days of January 3, 2021. We did not deem these shares outstanding, however, for the purpose of computing the percentage ownership of any other person. In computing the number of shares of our common stock beneficially owned by each selling stockholder, we did not deem outstanding any shares of common stock issuable upon the exercise of Warrants because the Warrants are not exercisable until June 8, 2021. The inclusion of any shares in this table does not constitute an admission of beneficial ownership for any selling stockholder named below.

Name of Selling Stockholder	Shares of Common Stock Beneficially Owned Prior to Offering		Number of Shares of Common Stock Being Offered(1)	Shares of Common Stock to be Beneficially Owned After Offering(2)	
	Number	Percentage		Number	Percentage
Entities affiliated with Bain Capital Life Sciences(3)	5,000,000	8.9%	6,250,000	—	—
Ally Bridge MedAlpha Master Fund L.P.(4)	2,642,500	4.7%	1,953,125	1,080,000	1.9%
OrbiMed Partners Master Fund Limited(5)	1,562,500	2.8%	1,953,125	—	—
Omega Fund VI, L.P.(6)	1,562,500	2.8%	1,953,125	—	—
Persons and entities affiliated with EcoR1 Capital, LLC(7)	1,000,000	1.8%	1,250,000	—	—
Samsara BioCapital, L.P.(8)	2,032,949	3.6%	781,250	1,407,949	2.5%

- (1) The number of shares of our Common Stock in the column “Number of Shares of Common Stock Being Offered” represents all of the shares of our common stock that a selling stockholder may offer and sell from time to time under this prospectus.

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- (2) 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 might sell 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, including common stock issuable upon exercise of the Warrants and pre-funded warrants issued or issuable in the Private Placement.
- (3) The shares reported under “Shares of Common Stock Beneficially Owned Prior to the Offering” consists of (i) 3,565,714 shares of common stock and 891,429 shares of common stock issuable upon exercise of pre-funded warrants, in each case held by Bain Capital Life Sciences Fund II, L.P. (“BCLS II”) and (ii) 434,286 shares of common stock and 108,571 shares of common stock issuable upon exercise of pre-funded warrants, in each case held by BCIP Life Sciences Associates, LP (“BCIPLS”) and, together with BCLS II, the “Bain Capital Life Science Entities”). In addition to the foregoing shares, as of January 3, 2021, BCLS II held Warrants to purchase 1,114,286 shares of common stock and BCIPLS held Warrants to purchase 135,714 shares of common stock that are not included in the shares reported under “Shares of Common Stock Beneficially Owned Prior to the Offering” because they are not exercisable until June 8, 2021. The shares reported under “Number of Shares of Common Stock Being Offered” consist of (i) the shares reported as beneficially owned by the Bain Capital Life Science Entities under “Shares of Common Stock Beneficially Owned Prior to the Offering” and (ii) the shares issuable upon exercise of Warrants held by the Bain Capital Life Science Entities described above, in each case, without giving effect to the Beneficial Ownership Limitation. Bain Capital Life Sciences Investors, LLC (“BCLSI”), whose managers are Jeffrey Schwartz and Adam Koppel, is the ultimate general partner of BCLS II and governs the investment strategy and decision-making process with respect to investments held by BCIPLS. As a result, each of BCLSI, Mr. Schwartz and Dr. Koppel may be deemed to share voting and dispositive power with respect to the shares of common stock held by the Bain Capital Life Sciences Entities. The address of the Bain Capital Life Sciences Entities is c/o Bain Capital Life Sciences, LP, 200 Clarendon Street, Boston, MA 02116.
- (4) The shares reported under “Shares of Common Stock Beneficially Owned Prior to the Offering” consists of 2,642,500 shares of common stock held by Ally Bridge MedAlpha Master Fund L.P. (“Ally Bridge”). In addition to the foregoing shares, as of January 3, 2021, Ally Bridge held Warrants to purchase 390,625 shares of common stock that are not included in the shares reported under “Shares of Common Stock Beneficially Owned Prior to the Offering” because they are not exercisable until June 8, 2021. The shares reported under “Number of Shares of Common Stock Being Offered” consist of (i) 1,562,500 shares of common stock purchased by Ally Bridge in the Private Placement and (ii) the shares issuable upon exercise of Warrants held by Ally Bridge described above. Mr. Fan Yu is the sole shareholder of ABG Management Ltd., which is the sole member of each of Ally Bridge MedAlpha Management GP, LLC and Ally Bridge Group (NY) LLC. Ally Bridge Group (NY) LLC and Ally Bridge MedAlpha Management L.P., acting through its general partner Ally Bridge MedAlpha Management GP, LLC, manage Ally Bridge’s investments. As such, each of the foregoing entities and Mr. Fan Yu may be deemed to share beneficial ownership of the shares held of record by Ally Bridge. Each of them disclaims any such beneficial ownership. The address of Ally Bridge is c/o Ally Bridge Group (NY) LLC, 430 Park Avenue, 12<sup>th</sup> Floor, New York, NY 10022.
- (5) The shares reported under “Shares of Common Stock Beneficially Owned Prior to the Offering” consists of 1,562,500 shares of common stock held by OrbiMed Partners Master Fund Limited (“OrbiMed”). In addition to the foregoing shares, as of January 3, 2021, OrbiMed held Warrants to purchase 390,625 shares of common stock that are not included in the shares reported under “Shares of Common Stock Beneficially Owned Prior to the Offering” because they are not exercisable until June 8, 2021. The shares reported under “Number of Shares of Common Stock Being Offered” consist of (i) the shares reported as beneficially owned by OrbiMed under “Shares of Common Stock Beneficially Owned Prior to the Offering” and (ii) the shares issuable upon exercise of Warrants held by OrbiMed described above. OrbiMed Capital LLC (“OrbiMed Capital”) is the investment advisor for OrbiMed. OrbiMed Capital is a relying advisor of OrbiMed Advisors LLC. OrbiMed Advisors LLC and OrbiMed Capital exercise voting and investment

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power through a management committee comprised of Carl L. Gordon, Sven H. Borho, and Jonathan T. Silverstein, each of whom disclaims beneficial ownership of the shares held by OrbiMed. The address of OrbiMed is c/o OrbiMed Capital LLC, 601 Lexington Avenue, 54<sup>th</sup> Floor, New York, NY 10022.

- (6) The shares reported under “Shares of Common Stock Beneficially Owned Prior to the Offering” consists of 1,562,500 shares of common stock held by Omega Fund VI, L.P. (“Omega Fund”). In addition to the foregoing shares, as of January 3, 2021, Omega Fund held Warrants to purchase 390,625 shares of common stock that are not included in the shares reported under “Shares of Common Stock Beneficially Owned Prior to the Offering” because they are not exercisable until June 8, 2021. The shares reported under “Number of Shares of Common Stock Being Offered” consist of (i) the shares reported as beneficially owned by Omega Fund under “Shares of Common Stock Beneficially Owned Prior to the Offering” and (ii) the shares issuable upon exercise of Warrants held by Omega Fund described above. Omega Fund VI GP Manager, Ltd. (“Omega Ltd.”) serves as the general partner of Omega Fund VI GP, L.P. (“Omega GP”), which serves as the general partner of Omega Fund; and each of Omega Ltd. and Omega GP may be deemed to own beneficially the shares held by Omega Fund. Claudio Nessi, Otello Stampacchia and Anne-Mari Paster are the directors of Omega Ltd and may be deemed to beneficially own the shares held directly by Omega Fund. The address for Omega Fund is 888 Boylston Street, Suite 1111, Boston, MA 02199.
- (7) The shares reported under “Shares of Common Stock Beneficially Owned Prior to the Offering” consists of (i) 153,700 shares of common stock held by EcoR1 Capital Fund, L.P. (“EcoR1 Capital”) and (ii) 846,300 shares of common stock held by EcoR1 Capital Fund Qualified, L.P. (“EcoR1 Qualified” and together with EcoR1 Capital, the “EcoR1 Funds”). In addition to the foregoing shares, as of January 3, 2021, EcoR1 Capital held Warrants to purchase 38,425 shares of common stock and EcoR1 Qualified held Warrants to purchase 211,575 shares of common stock that are not included in the shares reported under “Shares of Common Stock Beneficially Owned Prior to the Offering” because they are not exercisable until June 8, 2021. The shares reported under “Number of Shares of Common Stock Being Offered” consist of (i) the shares reported as beneficially owned by the EcoR1 Funds under “Shares of Common Stock Beneficially Owned Prior to the Offering” and (ii) the shares issuable upon exercise of Warrants held by the EcoR1 Funds described above. Oleg Nodelman directly or indirectly controls the EcoR1 Funds and as a result may be deemed to have voting and dispositive power over the securities held directly by the EcoR1 Funds. The address for the EcoR1 Funds is 357 Tehama Street, Suite 3, San Francisco, CA 94103.
- (8) The shares reported under “Shares of Common Stock Beneficially Owned Prior to the Offering” consists of (i) 1,899,616 shares of common stock held by Samsara BioCapital, L.P. (“Samsara LP”) and (ii) 133,333 shares of common stock that may be acquired by Samsara LP upon exercise of warrants purchased in April 2019. In addition to the foregoing shares, as of January 3, 2021, Samsara LP held Warrants to purchase 156,250 shares of common stock that are not included in the shares reported under “Shares of Common Stock Beneficially Owned Prior to the Offering” because they are not exercisable until June 8, 2021. The shares reported under “Number of Shares of Common Stock Being Offered” consist of (i) 625,000 shares of common stock purchased by Samsara LP in the Private Placement and (ii) the shares issuable upon exercise of Warrants held by Samsara described above. The general partner of Samsara LP is Samsara BioCapital GP, LLC (“Samsara LLC”). Dr. Srinivas Akkaraju, MD, PhD is the managing member of Samsara LLC and is a member of our board of directors. Dr. Akkaraju may be deemed to have voting and investment power of the securities held by Samsara LP and may be deemed to beneficially own certain shares held by Samsara LP. Dr. Akkaraju disclaims beneficial ownership of these shares, except to the extent of his pecuniary interest therein. The address for Samsara LP is 628 Middlefield Road, Palo Alto, CA 94301.

## PLAN OF DISTRIBUTION

The selling stockholders, which as used herein includes pledgees, assignees, donees, transferees or their respective successors-in-interest selling shares of common stock or interests in shares of common stock received after the date of this prospectus from a selling stockholder as a pledge, assignment, gift, partnership distribution or other transfer, may, from time to time, sell, transfer or otherwise dispose of any or all of their shares of common stock or interests in shares of common stock on any stock exchange, market or trading facility on which the shares are traded or in private transactions. These dispositions may be at fixed prices, at prevailing market prices at the time of sale, at prices related to the prevailing market price, at varying prices determined at the time of sale, or at negotiated prices.

The selling stockholders may use any one or more of the following methods when disposing of shares or interests therein:

- ordinary brokerage transactions and transactions in which the broker-dealer solicits purchasers;
- block trades in which the broker-dealer will attempt to sell the shares as agent, but may position and resell a portion of the block as principal to facilitate the transaction;
- purchases by a broker-dealer as principal and resale by the broker-dealer for its account;
- an exchange distribution in accordance with the rules of the applicable exchange;
- privately negotiated transactions;
- short sales effected after the date the registration statement of which this prospectus forms a part is declared effective by the SEC;
- through the writing or settlement of options or other hedging transactions, whether through an options exchange or otherwise;
- broker-dealers may agree with the selling stockholders to sell a specified number of such shares at a stipulated price per share;
- a combination of any such methods of sale; and
- any other method permitted by applicable law.

The selling stockholders may, from time to time, pledge or grant a security interest in some or all of the shares of common stock owned by them and, if they default in the performance of their secured obligations, the pledgees or secured parties may offer and sell the shares of common stock, from time to time, under this prospectus, or under an amendment to this prospectus under Rule 424(b)(3) or other applicable provision of the Securities Act of 1933, as amended (the "Securities Act"), amending the list of selling stockholders to include the pledgee, transferee or other successors-in-interest as selling stockholders under this prospectus. The selling stockholders also may transfer the shares of common stock in other circumstances, in which case the transferees, pledgees or other successors-in-interest will be the selling beneficial owners for purposes of this prospectus.

In connection with the sale of our common stock or interests therein, the selling stockholders may enter into hedging transactions with broker-dealers or other financial institutions, which may in turn engage in short sales of the common stock in the course of hedging the positions they assume. The selling stockholders may also sell shares of our common stock short and deliver these securities to close out their short positions, or loan or pledge the common stock to broker-dealers that in turn may sell these securities. The selling stockholders may also enter into option or other transactions with broker-dealers or other financial institutions or the creation of one or more derivative securities 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).

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The aggregate proceeds to the selling stockholders from the sale of the common stock offered by them will be the purchase price of the common stock less discounts or commissions, if any. Each of the selling stockholders reserves the right to accept and, together with their agents from time to time, to reject, in whole or in part, any proposed purchase of common stock to be made directly or through agents. We will not receive any of the proceeds from this offering. Upon any exercise of the pre-funded warrants or Warrants by payment of cash, however, we will receive the exercise price of the pre-funded warrants or Warrants.

The selling stockholders also may resell all or a portion of the shares in open market transactions in reliance upon Rule 144 under the Securities Act, provided that they meet the criteria and conform to the requirements of that rule.

The selling stockholders and any underwriters, broker-dealers or agents that participate in the sale of the common stock or interests therein may be “underwriters” within the meaning of Section 2(a)(11) of the Securities Act. Any discounts, commissions, concessions or profit they earn on any resale of the shares may be underwriting discounts and commissions under the Securities Act. Selling stockholders who are “underwriters” within the meaning of Section 2(a)(11) of the Securities Act will be subject to the prospectus delivery requirements of the Securities Act.

To the extent required, the shares of our common stock to be sold, the names of the selling stockholders, the respective purchase prices and public offering prices, the names of any agents, dealer or underwriter, and any applicable commissions or discounts with respect to a particular offer will be set forth in an accompanying prospectus supplement or, if appropriate, a post-effective amendment to the registration statement that includes this prospectus.

In order to comply with the securities laws of some states, if applicable, the common stock may be sold in these jurisdictions only through registered or licensed brokers or dealers. In addition, in some states the common stock may not be sold unless it has been registered or qualified for sale or an exemption from registration or qualification requirements is available and is complied with.

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, to the extent applicable, we will make copies of this prospectus (as it may be supplemented or amended from time to time) 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.

We have agreed to indemnify the selling stockholders against liabilities, including liabilities under the Securities Act and state securities laws, relating to the registration of the shares offered by this prospectus.

We have agreed with the selling stockholders to use commercially reasonable efforts to cause the registration statement of which this prospectus forms a part to remain continuously effective until the earlier of (1) such time as all of the shares covered by this prospectus have been disposed of pursuant to and in accordance with such registration statement or (2) 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 by this prospectus has been passed upon 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, 2019, 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. Our SEC filings are also available to you on the SEC's Internet site at [www.sec.gov](http://www.sec.gov).

We make available, free of charge, through our investor relations website, our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, statements of changes in beneficial ownership of securities and amendments to those reports and statements as soon as reasonably practicable after they are filed with the SEC. The address for our website is <http://www.syros.com>. The contents on our website are not part of this prospectus, and the reference to our website does not constitute incorporation by reference into this prospectus of the information contained at that site.

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

## 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, 2019, filed with the SEC on March 5, 2020 (including information specifically incorporated by reference therein from our [Proxy Statement](#) filed with the SEC on April 28, 2020);
- (2) Our Quarterly Report on [Form 10-Q](#) for the quarter ended March 31, 2020, filed with the SEC on May 7, 2020;
- (3) Our Quarterly Report on [Form 10-Q](#) for the quarter ended June 30, 2020, filed with the SEC on August 6, 2020;
- (4) Our Quarterly Report on [Form 10-Q](#) for the quarter ended September 30, 2020, filed with the SEC on November 5, 2020;
- (5) Our Current Reports on Form 8-K filed with the SEC on [January 13, 2020](#) (except Item 7.01), [February 13, 2020](#), [June 12, 2020](#), [September 9, 2020](#), [October 26, 2020](#), [December 7, 2020](#) (except Item 7.01), [December 8, 2020](#) and [December 23, 2020](#);
- (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.  
35 CambridgePark Drive, 4th Floor  
Cambridge, Massachusetts, 02140  
Attention: Gerald E. Quirk, Chief Legal and Administrative Officer & Secretary  
Telephone: (617) 744-1340

**14,140,625 Shares**



**Common Stock**

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**PROSPECTUS**

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, 2021

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PART II

INFORMATION NOT REQUIRED IN PROSPECTUS

**Item 14. Other Expenses of Issuance and Distribution.**

The following table sets forth the various expenses to be incurred in connection with the sale and distribution of the securities being registered hereby, all of which will be borne by the Registrant (except 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). All amounts shown are estimates except the SEC registration fee.

SEC registration fee	\$ 16,122
Accounting fees and expenses	10,000
Legal fees and expenses	40,000
Miscellaneous fees and expenses	3,878
Total	<u>\$ 70,000</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 of any action alleged to have been taken or omitted in such

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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 (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.

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### **Item 16. Exhibits**

<u>Exhibit No.</u>	<u>Description</u>
4.1	<a href="#"><u>Restated Certificate of Incorporation of the Registrant, including the Certificate of Designation of Preferences, Rights and Limitations of Series A Convertible Preferred Stock of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant's Quarterly Report on Form 10-Q for the quarter ended March 31, 2019 filed with the SEC on May 1, 2019 (FileNo. 001-37813)).</u></a>
4.2	<a href="#"><u>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)).</u></a>
4.3	<a href="#"><u>Form of Common Stock Certificate (incorporated by reference to Exhibit 4.1 to the Registrant's FormS-1 filed with the SEC on June 3, 2016 (File No. 333-211818)).</u></a>
4.4	<a href="#"><u>Form of Warrant to Purchase Common Stock or Pre-Funded Warrants (incorporated by reference to Exhibit 4.1 to the Registrant's Current Report on Form 8-K filed with the SEC on December 7, 2020 (FileNo. 001-37813)).</u></a>
4.5	<a href="#"><u>Form of Pre-Funded Warrant (incorporated by reference to Exhibit 4.2 to the Registrant's Current Report on Form 8-K filed with the SEC on December 7, 2020 (File No. 001-37813)).</u></a>
4.6	<a href="#"><u>Securities Purchase Agreement, dated December 4, 2020, by and among the Registrant and the persons party thereto (incorporated by reference to Exhibit 10.1 to the Registrant's Current Report on Form 8-K filed with the SEC on December 7, 2020 (File No. 001-37813)).</u></a>
4.7	<a href="#"><u>Registration Rights Agreement, dated December 4, 2020, by and among the Registrant and the persons party thereto (incorporated by reference to Exhibit 10.2 to the Registrant's Current Report on Form 8-K filed with the SEC on December 7, 2020 (File No. 001-37813)).</u></a>
5.1	<a href="#"><u>Opinion of Wilmer Cutler Pickering Hale and Dorr LLP.</u></a>
23.1	<a href="#"><u>Consent of Ernst &amp; Young LLP, independent registered public accounting firm for the Registrant.</u></a>
23.2	<a href="#"><u>Consent of Wilmer Cutler Pickering Hale and Dorr LLP (included in Exhibit 5.1).</u></a>
24.1	<a href="#"><u>Powers of Attorney (included in the signature pages to the Registration Statement).</u></a>

### **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 the 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
  - (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;

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*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 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 Securities and Exchange Commission 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 Registration Statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Cambridge, Commonwealth of Massachusetts, on this 7<sup>th</sup> day of January, 2021.

**SYROS PHARMACEUTICALS, INC.**

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

**SIGNATURES AND POWER OF ATTORNEY**

We, the undersigned officers and directors of Syros Pharmaceuticals, Inc. hereby severally constitute and appoint Nancy Simonian, Joseph J. Ferra, Jr. and Gerald Quirk, and each of them singly, our true and lawful attorneys with full power to any of them, and to each of them singly, to sign for us and in our names in the capacities indicated below the Registration Statement on Form S-3 filed herewith and any and all pre-effective and post-effective amendments to said Registration Statement and generally to do all such things in our name and behalf in our capacities as officers and directors to enable Syros Pharmaceuticals, Inc. to comply with the provisions of the Securities Act of 1933, as amended, and all requirements of the Securities and Exchange Commission, hereby ratifying and confirming our signatures as they may be signed by our said attorneys, or any of them, to said Registration Statement and any and all amendments thereto.

Pursuant to the requirements of the Securities Act of 1933, as amended, this 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>
<u>/s/ Nancy Simonian</u> Nancy Simonian, M.D.	President, Chief Executive Officer and Director (Principal Executive Officer)	January 7, 2021
<u>/s/ Joseph J. Ferra</u> Joseph J. Ferra, Jr.	Chief Financial Officer (Principal Financial and Accounting Officer)	January 7, 2021
<u>/s/ Srinivas Akkaraju</u> Srinivas Akkaraju, M.D., Ph.D.	Director	January 7, 2021
<u>/s/ Mark J. Alles</u> Mark J. Alles	Director	January 7, 2021
<u>/s/ S. Gail Eckhardt</u> S. Gail Eckhardt, M.D.	Director	January 7, 2021
<u>/s/ Marsha H. Fanucci</u> Marsha H. Fanucci	Director	January 7, 2021
<u>Amir Nashat, Ph.D.</u>	Director	



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<u>Signature</u>	<u>Title</u>	<u>Date</u>
<u>/s/ Phillip A. Sharp</u> Phillip A. Sharp, Ph.D.	Director	January 7, 2021
<u>/s/ Peter Wirth</u> Peter Wirth	Director	January 7, 2021
<u>/s/ Richard A. Young</u> Richard A. Young, Ph.D.	Director	January 7, 2021

January 7, 2021

+1 617 526 6000 (t)

+1 617 526 5000 (f)

wilmerhale.com

Syros Pharmaceuticals, Inc.  
35 CambridgePark Drive, 4th Floor  
Cambridge, MA 02140

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 14,140,625 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 Stockholders"). The Shares consist of (i) 10,312,500 outstanding shares of Common Stock (the "Outstanding Shares") that are held by the Selling Stockholders, (ii) 1,000,000 shares of Common Stock issuable upon the exercise of outstanding pre-funded warrants to purchase shares of Common Stock and (iii) 2,828,125 shares of Common Stock issuable upon the exercise of outstanding warrants to purchase shares of Common Stock (the "Warrants") (or issuable upon exercise of pre-funded warrants to purchase shares of Common Stock that are issuable to holders of Warrants upon exercise of such warrants for pre-funded warrants in lieu of Common Stock) (collectively, the "Warrant Shares" and any and all pre-funded warrants described in clauses (ii) and (iii), the "Pre-Funded Warrants") that are held by the Selling Stockholders.

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 Outstanding Shares being fully paid, is based solely on a certificate of the Chief Financial Officer of the Company confirming the Company's receipt of the consideration called for by the applicable resolutions authorizing the issuance of such Outstanding Shares.

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 San Francisco Washington

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

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 (i) the Outstanding Shares have been duly authorized for issuance and are validly issued, fully paid and nonassessable, and (ii) the Warrant Shares have been duly authorized for issuance and, when issued, delivered and paid for in accordance with the terms of the Pre-Funded Warrants or Warrants, as applicable, including the payment of the exercise price therefor, will be 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 T. Mazareas  
Cynthia T. Mazareas, a Partner

**Consent of Independent Registered Public Accounting Firm**

We consent to the reference to our firm under the caption “Experts” in this RegistrationStatement (Form S-3) and related Prospectus of Syros Pharmaceuticals, Inc. for the registration of shares of its common stock and to the incorporation by reference therein of our report dated March 5, 2020, with respect to the consolidated financial statements of Syros Pharmaceuticals, Inc., included in its Annual Report (Form 10-K) for the year ended December 31, 2019, filed with the Securities and Exchange Commission.

/s/ Ernst & Young LLP

Boston, Massachusetts  
January 7, 2021