

PROSPECTUS

\$50,000,000

SYROS PHARMACEUTICALS, INC.



Common Stock

We have entered into a sales agreement, or the sales agreement, with Cowen and Company, LLC, or Cowen, dated April 6, 2023, relating to the sale of shares of our common stock, \$0.001 par value per share, offered by this prospectus. In accordance with the terms of the sales agreement, we may offer and sell shares of our common stock having an aggregate offering price of up to \$50.0 million from time to time through Cowen, acting as our agent or principal. Upon entry into the sales agreement, we terminated our prior at-the-market program pursuant to the original sales agreement, dated July 12, 2020, or the original agreement. At the time of such termination, \$75.0 million out of an aggregate of \$75.0 million remained unsold under the original agreement.

Our common stock is listed on The Nasdaq Global Select Market under the symbol "SYRS." The last reported sale price of our common stock on April 4, 2023 was \$2.65 per share.

Sales of our common stock, if any, under this prospectus will be made at market prices by any method that is deemed an "at the market offering" as defined in Rule 415(a)(4) promulgated under the Securities Act of 1933, as amended, or the Securities Act. Cowen is not required to sell any specific amount of securities, but will act as our sales agent using commercially reasonable efforts consistent with its normal trading and sales practices and applicable state and federal laws, rules and regulations and the rules of The Nasdaq Stock Market, LLC. There is no arrangement for funds to be received in any escrow, trust or similar arrangement.

Cowen will be entitled to compensation at a commission rate up to 3.0% of the gross sales price per share sold under the sales agreement. See "Plan of Distribution" beginning on page 16 for additional information regarding the compensation to be paid to Cowen. In connection with the sale of the common stock on our behalf, Cowen will be deemed to be an "underwriter" within the meaning of the Securities Act and the compensation of Cowen will be deemed to be underwriting commissions or discounts. We have also agreed to provide indemnification and contribution to Cowen with respect to certain liabilities, including liabilities under the Securities Act.

Investing in these securities involves certain risks. See "[Risk Factors](#)" on page 9 of this prospectus and in the documents incorporated by reference in this prospectus for a discussion of the factors you should carefully consider before deciding to purchase our common stock.

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.

TD Cowen

The date of this prospectus is April 28, 2023

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission, or SEC, utilizing a shelf registration process. Under the shelf registration process, we may offer shares of our common stock having an aggregate offering price of up to \$50.0 million from time to time under this prospectus at prices and on terms to be determined by market conditions at the time of offering.

This prospectus describes the specific terms of the common stock we are offering and also adds to, and updates information contained in the documents incorporated by reference into this prospectus. To the extent there is a conflict between the information contained in this prospectus, on the one hand, and the information contained in any document incorporated by reference into this prospectus that was filed with the SEC before the date of this prospectus, on the other hand, you should rely on the information in this prospectus. If any statement in one of these documents is inconsistent with a statement in another document having a later date — for example, a document incorporated by reference into this prospectus — the statement in the document having the later date modifies or supersedes the earlier statement.

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

You should rely only on the information contained in or incorporated by reference in this prospectus and in any free writing prospectus we have authorized for use in connection with this offering. We have not, and Cowen has not, authorized anyone to provide any information other than that contained or incorporated by reference in this prospectus or in any free writing prospectus prepared by or on behalf of us or to which we have referred you. We and Cowen take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We are not, and Cowen is not, making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus, in the documents incorporated by reference in this prospectus, and in any free writing prospectus prepared by or on behalf of us that we have authorized for use in connection with this offering is accurate only as of the date of those respective documents. Our business, financial condition, results of operations and prospects may have changed since those dates. You should read this prospectus, the documents incorporated by reference in this prospectus, and any free writing prospectus prepared by or on behalf of us that we have authorized for use in connection with this offering, in their entirety before making an investment decision. You should also read and consider the information in the documents we have referred you to in the sections of this prospectus entitled “Where You Can Find More Information” and “Incorporation by Reference.”

Other than in the United States, no action has been taken by us or Cowen that would permit a public offering of the securities offered by this prospectus in any jurisdiction where action for that purpose is required. The securities offered by this prospectus may not be offered or sold, directly or indirectly, nor may this prospectus or any other offering material or advertisements in connection with the offer and sale of any such securities be distributed or published in any jurisdiction, except under circumstances that will result in compliance with the applicable rules and regulations of that jurisdiction. Persons into whose possession this prospectus comes are advised to inform themselves about and to observe any restrictions relating to the offering and the distribution of this prospectus. This prospectus does not constitute an offer to sell or a solicitation of an offer to buy any securities offered by this prospectus in any jurisdiction in which such an offer or a solicitation is unlawful.

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

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

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at <http://www.sec.gov>. Copies of certain information filed by us with the SEC are also available on our website at www.syros.com. Our website is not a part of this prospectus and is not incorporated by reference in this prospectus.

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

INCORPORATION BY REFERENCE

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

- Annual Report on [Form 10-K](#) for the fiscal year ended December 31, 2022, as filed with SEC on March 2, 2023 including the information specifically incorporated by reference into the Annual Report on Form 10-K from our [definitive proxy statement](#) for the 2023 Annual Meeting of Stockholders, as filed with the SEC on April 21, 2023;
- Current Report on Form 8-K filed [January 9, 2023](#) (other than the information furnished under Item 7.01 therein); and
- The description of our common stock contained in our Registration Statement on [Form 8-A/A](#) filed on July 20, 2017, as updated by [Exhibit 4.1](#) to our Annual Report on Form 10-K for the fiscal year ended December 31, 2022, and including any amendments and reports filed for the purpose of updating such description.

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

Syros Pharmaceuticals, Inc.
35 CambridgePark Drive, 4th Floor
Cambridge, Massachusetts, 02140
Attention: Gerald E. Quirk, Chief Legal Officer
Telephone: (617) 744-1340

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS AND MARKET DATA

This prospectus and the information incorporated by reference in this prospectus include “forward-looking statements” within the meaning of Section 27A of the Securities Act, and Section 21E of the Exchange Act. All statements, other than statements of historical facts, contained in this prospectus or incorporated by reference herein, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of management and expected market growth are forward-looking statements. The words “anticipate,” “believe,” “continue,” “could,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “would” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. In addition, statements that “we believe” and similar statements reflect our beliefs and opinions on the relevant subject. The forward-looking statements and opinions contained in this prospectus and incorporated by reference herein are based upon information available to us as of the date such statements are made and, while we believe such information forms a reasonable basis for such statements at the time made, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These forward-looking statements include, among other things, statements about:

- our plans to initiate 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 tamibarotene, SY-2101 and SY-5609;
- our planned clinical trials for our product candidates, whether conducted by us or by any 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 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 into investigational new drug application-enabling studies under our sickle cell disease collaboration with Global Blood Therapeutics, Inc., or 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, or 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 collaboration;
- developments relating to our competitors and our industry;
- the impact of government laws and regulations;

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- the timing of and our ability to file new drug applications and obtain and maintain regulatory approvals for our product candidates;
- the rate and degree of market acceptance and clinical utility of any products for which we receive marketing approval;
- our commercialization, marketing and manufacturing capabilities and strategy;
- our intellectual property position and strategy;
- our ability to identify additional products or product candidates with significant commercial potential;
- our expectations related to the use of our current cash, cash equivalents and marketable securities and the period of time in which such capital will be sufficient to fund our planned operations;
- our estimates regarding expenses, future revenue, capital requirements and need for additional financing; general economic conditions, including inflation, recession risk and increasing interest rates; and
- other risks and uncertainties, including those listed under the caption “Risk Factors” in our most recent Annual Report on Form 10-K and other filings we make with the SEC.

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 that could cause actual results or events to differ materially from the forward-looking statements that we make, particularly the factors discussed below under “Risk Factors”.

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.

SYROS PHARMACEUTICALS, INC.

This summary highlights information contained elsewhere in this prospectus and does not contain all of the information that you should consider in making your investment decision. Before investing in our common stock, you should carefully consider, among other things, our financial statements and the related notes and the sections titled "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" included elsewhere or incorporated by reference in this prospectus. Unless otherwise stated, all references to "us," "our," "Syros," "Syros Pharmaceuticals," "we," the "Company" and similar designations refer to Syros Pharmaceuticals, Inc.

Overview

We are a biopharmaceutical company committed to developing new standards of care for the frontline treatment of patients with hematologic malignancies. Driven by the motivation to help patients with blood disorders that have largely eluded other targeted approaches, we are advancing a late-stage clinical pipeline which includes product candidates targeting multiple hematology indications.

Corporate Information

We were incorporated under the laws of the State of Delaware on November 9, 2011 under the name LS22, Inc. Our principal executive offices are located at 35 CambridgePark Drive, 4th Floor, Cambridge, Massachusetts 02140, and our telephone number is (617) 744-1340. Our internet address is www.syros.com. The information on our web site is not incorporated by reference into this prospectus and should not be considered to be a part of this prospectus. Our internet address is included in this prospectus as an inactive textual reference only. We changed our name to Syros Pharmaceuticals, Inc. on August 15, 2012.

Implications of Being a Smaller Reporting Company

We are a smaller reporting company as defined under Rule 405 of the Securities Act and, as such, are subject to certain reduced public company reporting requirements. Accordingly, the information contained herein may be different than the information you receive from other public companies in which you hold stock.

THE OFFERING

Common stock offered by us	Shares of our common stock having an aggregate offering price of up to \$50.0 million.
Common stock to be outstanding after this offering assuming the sale of all shares in this offering	Up to 39,131,041 shares, assuming sales at a price of \$2.65 per share, which was the closing price of our common stock on The Nasdaq Global Select Market on April 4, 2023. The actual number of shares issued will vary depending on the sales price under this offering.
Plan of Distribution	“At the market offering” that may be made from time to time through our sales agent, Cowen. See the section entitled “Plan of Distribution” on page 16 of this prospectus.
Use of Proceeds	<p>We intend to use the net proceeds from the sale of any securities offered under this prospectus for general corporate purposes. Although we have not yet identified specific uses for these proceeds, we currently anticipate using the proceeds for some or all of the following purposes: research and development expenses, acquisitions or in-licenses of complementary companies, products, product candidates or technologies, expenditures to build out our development and commercial capabilities, repayment and refinancing of debt, working capital and capital expenditures.</p> <p>We may temporarily invest the net proceeds in short-term, investment-grade, interest-bearing instruments and U.S. government securities until they are used for their stated purpose. We have not determined the amount of net proceeds to be used specifically for such purposes. As a result, management will retain broad discretion over the allocation of net proceeds of this offering. See “Use of Proceeds” on page 11 of this prospectus.</p>
Risk Factors	See “Risk Factors” beginning on page 9 of this prospectus and the other information included in, or incorporated by reference into, this prospectus for a discussion of certain factors you should carefully consider before deciding to invest in shares of our common stock.
Nasdaq Global Select Market symbol	“SYRS”

The number of shares of our common stock that will be outstanding immediately after this offering is based on 20,263,116 shares outstanding as of December 31, 2022. The number of shares outstanding as of December 31, 2022, as used throughout this prospectus, unless otherwise indicated, excludes:

- 1,727,237 shares of common stock issuable upon exercise of stock options outstanding as of December 31, 2022, at a weighted-average exercise price of \$39.94 per share;
- 1,204,421 shares of our common stock issuable upon the vesting of restricted stock units and restricted stock awards outstanding as of December 31, 2022;
- 14,142,298 shares of common stock issuable upon the exercise of warrants outstanding as of December 31, 2022, at a weighted average exercise price of \$12.06 per share;

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- 7,526,739 shares of common stock issuable upon exercise of pre-funded warrants outstanding as of December 31, 2022;
- 1,991,628 shares of common stock reserved as of December 31, 2022 for future issuance under our 2022 Equity Incentive Plan, as amended;
- 22,443 shares of common stock reserved for future issuance under our 2022 Inducement Stock Incentive Plan, as amended; and
- 237,169 shares of common stock reserved as of December 31, 2022 for future issuance under our 2016 Employee Stock Purchase Plan.

RISK FACTORS

An investment in our common stock involves a high degree of risk. Before deciding whether to invest in our common stock, you should consider carefully the risks and uncertainties described below and under the section captioned "Risk Factors" contained in our most recent Annual Report on Form 10-K and other filings we make with the SEC from time to time, which are incorporated by reference herein in their entirety, together with other information in this prospectus, the information and documents incorporated by reference in this prospectus, and in any prospectus supplement or free writing prospectus that we authorize for use in connection with this offering. If any of these risks actually occurs, our business, financial condition, results of operations or cash flow could suffer materially. In such event, the trading price of our common stock could decline and you might lose all or part of your investment.

Additional Risks Related to This Offering

If you purchase shares of common stock in this offering, you may suffer immediate dilution of your investment.

The shares sold in this offering, if any, will be sold from time to time at various prices. It is possible that the offering price of our common stock will be substantially higher than the net tangible book value per share of our common stock. Therefore, if you purchase shares of our common stock in this offering, you may pay a price per share that substantially exceeds our net tangible book value per share after this offering. In such event, you will experience immediate dilution representing the difference between the price you paid in this offering and our as adjusted net tangible book value per share after giving effect to the sales of shares in this offering at the applicable offering prices. To the extent outstanding options or warrants are exercised for shares of our common stock at exercise prices that are lower than the price you paid in this offering, you will incur further dilution.

You may experience future dilution as a result of future equity offerings.

We expect our expenses to remain high in connection with our planned operations. In order to raise additional capital, we may in the future offer additional shares of our common stock or other securities convertible into or exchangeable for our common stock at prices that may not be the same as the price per share in this offering. We may sell shares or other securities in any other offering at a price per share that is less than the price per share paid by investors in this offering, and investors purchasing shares or other securities in the future could have rights superior to existing stockholders. The price per share at which we sell additional shares of our common stock, or securities convertible or exchangeable into common stock, in future transactions may be higher or lower than the price per share paid by investors in this offering.

We have broad discretion over the use of our cash and cash equivalents, including the net proceeds we receive in this offering, and may not use them effectively.

We have not designated any portion of the net proceeds from this offering to be used for any particular purpose. Our management has broad discretion to use our cash and cash equivalents, including the net proceeds we receive in this offering, to fund our operations and could spend these funds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could have a material adverse effect on our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending their use to fund operations, we may invest our cash and cash equivalents in a manner that does not produce income or that loses value.

We do not intend to pay dividends in the foreseeable future.

We have never paid cash dividends on our common stock. We currently intend to retain our future earnings, if any, to finance the operation and growth of our business and currently do not plan to pay any cash dividends in the foreseeable future. In addition, debt financing, such as our term loan facility with Oxford Finance LLC, or

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Oxford, as collateral agent and lender, that we originally entered into on February 12, 2020, as amended, has created fixed payment obligations and imposed restrictive covenants that limit our ability to take specific actions, such as incurring additional debt, making capital expenditures, creating liens, redeeming stock or declaring dividends, that could adversely impact our ability to conduct our business. The terms of our term loan facility with Oxford precludes us from paying cash dividends to our stockholders without Oxford's consent. As a result, only appreciation of the price of our common stock will provide a return to stockholders for the foreseeable future.

Sales of a significant number of shares of our common stock in the public markets, or the perception that such sales could occur, could depress the market price of our common stock.

Sales of a substantial number of shares of our common stock in the public markets, or the perception that such sales could occur, could depress the market price of our common stock and impair our ability to raise capital through the sale of additional equity securities. We have agreed, subject to certain exceptions set forth in the sales agreement, to provide Cowen with notice as promptly as reasonably possible before we offer to sell, contract to sell, sell, grant any option to sell or otherwise dispose of any common stock or securities convertible into or exchangeable for shares of common stock, warrants or any rights to purchase or acquire common stock during the pendency of any placement notice delivered by us to Cowen under the sales agreement, and for five trading days following the termination of such placement notice. Therefore, it is possible that we could issue and sell additional shares of our common stock in the public markets. We cannot predict the effect that future sales of our common stock would have on the market price of our common stock.

The common stock offered hereby will be sold in "at the market offerings," and investors who buy shares at different times will likely pay different prices.

Investors who purchase shares in this offering at different times will likely pay different prices, and accordingly may experience different levels of dilution and different outcomes in their investment results. We will have discretion, subject to market demand and the terms of the sales agreement, to vary the timing, prices and number of shares sold in this offering. In addition, subject to the final determination by our board of directors or any restrictions we may place in any applicable placement notice, there is no minimum or maximum sales price for shares to be sold in this offering. Investors may experience a decline in the value of the shares they purchase in this offering as a result of sales made at prices lower than the prices they paid.

The actual number of shares we will issue under the sales agreement and gross proceeds resulting from those sales, at any one time or in total, is uncertain.

Subject to certain limitations in the sales agreement and compliance with applicable law, we have the discretion to deliver placement notices to Cowen, at any time throughout the term of the sales agreement. The number of shares that are sold by Cowen after delivering a placement notice will fluctuate based on the market price of our common stock during the sales period and limits we set with Cowen. Because the price per share of each share sold will fluctuate based on the market price of our common stock during the sales period, it is not possible at this stage to predict the number of shares that will be ultimately issued or the gross proceeds to be raised in connection with those sales.

The trading price of our common stock is highly volatile, which could result in substantial losses for our stockholders.

The trading price of our common stock has been, and is likely to continue to be, highly volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. During the period from January 1, 2022 to April 4, 2023, the closing price of our common stock ranged from a high of \$38.00 per share to a low of \$2.56 per share. The stock market in general and the market for smaller pharmaceutical and biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, you may not be able to sell your common stock at or above the price you paid for your common stock in this offering.

USE OF PROCEEDS

We may issue and sell shares of our common stock having aggregate gross sales proceeds of up to \$50.0 million from time to time (before deducting sales agent commissions and expenses). Because there is no minimum offering amount required as a condition to close this offering, the actual total public offering amount, commissions and proceeds to us, if any, are not determinable at this time.

We intend to use the net proceeds from the sale of any shares of common stock offered under this prospectus for general corporate purposes. Although we have not yet identified specific uses for these proceeds, we currently anticipate using the proceeds for some or all of the following purposes:

- research and development expenses;
- acquisitions or in-licenses of complementary companies, products, product candidates or technologies;
- expenditures to build out our development and commercial capabilities;
- repayment and refinancing of debt;
- working capital; and
- capital expenditures.

The amounts and timing of our actual use of the net proceeds may vary significantly depending on numerous factors, including the progress of our research and development efforts, the status of and results from clinical trials, any collaborations that we may enter into with third parties for our programs, and any unforeseen cash needs. As of the date of this prospectus, we cannot specify with certainty all of the particular uses for the net proceeds to us from this offering. Accordingly, our management will have broad discretion in the timing and application of these proceeds. We do not expect that the net proceeds from this offering and our existing cash and cash equivalents will be sufficient to enable us to fund the completion of development of any product candidates we may develop.

Pending application of the net proceeds as described above, we intend to invest the net proceeds in short-term, investment-grade, interest-bearing instruments and U.S. government securities.

DESCRIPTION OF COMMON STOCK

Our authorized common stock consists of 70,000,000 shares of common stock, par value \$0.001 per share. The following description of our common stock and provisions of our restated certificate of incorporation and second amended and restated by-laws are summaries and are qualified by reference to our restated certificate of incorporation and our second amended and restated by-laws, copies of which are filed with the SEC as exhibits to our registration statement of which this prospectus forms a part.

Annual Meeting. Annual meetings of our stockholders are held on the date designated in accordance with our second amended and restated by-laws. Written notice must be mailed to each stockholder entitled to vote not less than ten nor more than 60 days before the date of the meeting. The presence in person, by means of remote communication in a manner authorized by the board of directors, or by proxy of the holders of a majority in voting power of the shares of our capital stock issued and outstanding and entitled to vote at the meeting constitutes a quorum for the transaction of business at meetings of the stockholders. Special meetings of stockholders may be called at any time by the board of directors, the chair of the board of directors or our Chief Executive Officer. Business transacted at any special meeting of stockholders shall be limited to matters relating to the purpose or purposes stated in the notice of meeting.

Voting Rights. Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. An election of directors by our stockholders is determined by a plurality of the votes cast by the stockholders entitled to vote on the election. Other matters are decided by the affirmative vote of our stockholders having a majority in voting power of the votes cast by the stockholders present or represented and voting on such matter, except as otherwise disclosed below.

Dividends. Subject to the rights, powers and preferences of any outstanding preferred stock, and except as provided by law or in our restated certificate of incorporation, dividends may be declared and paid or set aside for payment on the common stock out of legally available assets or funds when and as declared by the board of directors. The payment of dividends is contingent upon our revenue and earnings, capital requirements, and general financial condition, as well as contractual restrictions and other considerations deemed to be relevant by our board of directors.

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

Registration Rights

We have entered into three registration rights agreements with certain holders of our common stock, warrants and pre-funded warrants. These holders have the right to require us to register their shares under the Securities Act under specified circumstances. We refer to the shares with these registration rights as registrable securities. After registration pursuant to these rights, the registrable securities will become freely tradable without restriction under the Securities Act.

The registration rights agreements contain customary cross-indemnification provisions, pursuant to which we are obligated to indemnify the selling stockholders in the event of material misstatements or omissions in the registration statement attributable to us or any violation or alleged violation whether by action or inaction by us under the Securities Act, the Exchange Act, any state securities law or any rule or regulation promulgated under the Securities Act, the Exchange Act or any state securities law in connection with such registration statement or

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the qualification or compliance of the offering, and they are obligated to indemnify us for material misstatements or omissions in the registration statement attributable to them.

December 2020 Registration Rights Agreement

On December 4, 2020, we entered into a registration rights agreement with certain holders of our common stock, warrants and pre-funded warrants. Pursuant to the terms of this registration rights agreement, we agreed to file a registration statement covering the resale of the registrable securities within 30 days following the closing of the private placement in which the registrable securities were issued. We also agreed to use commercially reasonable efforts to cause such registration statement to become effective as soon as practicable and to keep such registration statement effective until the date the registrable securities covered by such registration statement have been sold or may be resold pursuant to Rule 144 without restriction. We agreed to be responsible for all fees and expenses incurred in connection with the registration of the registrable securities.

July 2022 Registration Rights Agreement and Affiliate Registration Rights Agreement

On July 3, 2022, we entered into a registration rights agreement with certain holders of our common stock, warrants and pre-funded warrants. Pursuant to the terms of this registration rights agreement, we agreed to file a registration statement covering the resale of the registrable securities within 30 days following the closing of the private placement in which the registrable securities were issued. We also agreed to use commercially reasonable efforts to cause such registration statement to become effective as soon as practicable and to keep such registration statement effective until the date the registrable securities covered by such registration statement have been sold or may be resold pursuant to Rule 144 without restriction. We agreed to be responsible for all fees and expenses incurred in connection with the registration of the registrable securities.

Also on July 3, 2022, we entered into an affiliate registration rights agreement with Baker Brothers Life Sciences, L.P. and 667, L.P., which we refer to as the Baker Funds. Pursuant to the terms of this affiliate registration rights agreement, following a request by the Baker Funds, we are obligated to file a resale registration statement on Form S-3, or other appropriate form, covering these registrable securities. We agreed to file such resale registration statement as promptly as reasonably practicable following such request, and in any event within sixty (60) days of such request. Our obligations to file such registration statement are subject to specified exceptions, and suspension and deferral rights as are set forth in this affiliate registration rights agreement. Under specified circumstances, we may also include securities of ours in any such registration statement. Under this affiliate registration rights agreement, the Baker Funds also have the right to one underwritten offering per calendar year, but no more than three underwritten offerings in total and not more than two underwritten offerings or “block trades” in any twelve month period, to effect the sale or distribution of the registrable securities, subject to specified exceptions, conditions and limitations.

Anti-Takeover Effects of Delaware Law and Our Charter and By-laws

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

Staggered Board; Removal of Directors

Our restated certificate of incorporation and our second amended and restated by-laws divide our board of directors into three classes with staggered three-year terms. In addition, a director may only be removed for cause and only by the affirmative vote of the holders of at least 75% of the votes that all of our stockholders would be entitled to cast in an annual election of directors. Any vacancy on our board of directors, including a vacancy

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resulting from an enlargement of our board of directors, may only be filled by vote of a majority of our directors then in office. The classification of our board of directors and the limitations on the removal of directors and filling of vacancies could make it more difficult for a third party to acquire, or discourage a third party from seeking to acquire, control of our company.

Stockholder Action by Written Consent; Special Meetings

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

Advance Notice Requirements for Stockholder Proposals

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

Exclusive Forum Selection

Our restated certificate of incorporation provides that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware (or, if the Court of Chancery of the State of Delaware does not have jurisdiction, the federal district court for the District of Delaware) shall, to the fullest extent permitted by law, be the sole and exclusive forum for (1) any derivative action or proceeding brought on our behalf, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers, other employees or stockholders to our company or our stockholders, (3) any action asserting a claim arising pursuant to any provision of the General Corporation Law of the State of Delaware, or the DGCL, or as to which the DGCL confers jurisdiction on the Court of Chancery of the State of Delaware or (4) any action asserting a claim arising pursuant to any provision of our restated certificate of incorporation or second amended and restated by-laws (in each case, as they may be amended from time to time) or governed by the internal affairs doctrine. This choice of forum provision will not apply to actions arising under the Securities Act, the Exchange Act or any other claim for which the federal courts have exclusive jurisdiction. Unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States of America shall, to the fullest extent permitted by law, be the sole and exclusive forum for the resolution of any claims arising under the Securities Act. Although our restated certificate of incorporation contains the choice of forum provisions described above, it is possible that a court could rule that such a provision is inapplicable for a particular claim or action or that such provision is unenforceable.

Delaware Business Combination Statute

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

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more of our outstanding voting stock and any entity or person affiliated with or controlling or controlled by such entity or person.

Amendment of Certificate of Incorporation and By-laws

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

Listing on The Nasdaq Global Select Market

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

Authorized but Unissued Shares

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

Transfer Agent and Registrar

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

PLAN OF DISTRIBUTION

We have entered into a sales agreement with Cowen, dated April 6, 2023, under which we may issue and sell from time to time up to an aggregate of \$50.0 million of shares of our common stock through Cowen as our sales agent or principal. Upon entry into the sales agreement, we terminated our prior at-the-market program pursuant to the original sales agreement, dated July 12, 2020, or the original agreement. At the time of such termination, the entire \$75.0 million remained unsold under the original agreement.

Sales of our common stock, if any, will be made at market prices by any method that is deemed to be an “at the market offering” as defined in Rule 415(a) (4) under the Securities Act, including sales made directly on The Nasdaq Global Select Market or any other trading market for our common stock. If authorized by us in writing, Cowen may purchase shares of our common stock as principal.

Cowen will offer our common stock subject to the terms and conditions of the sales agreement on a daily basis or as otherwise agreed upon by us and Cowen. We will designate the maximum amount of common stock to be sold through Cowen on a daily basis or otherwise determine such maximum amount together with Cowen. Subject to the terms and conditions of the sales agreement, Cowen will use its commercially reasonable efforts to sell on our behalf all of the shares of common stock requested to be sold by us. We may instruct Cowen not to sell shares of our common stock if the sales cannot be effected at or above the price designated by us in any such instruction. Cowen or we may suspend the offering of our common stock being made through Cowen under the sales agreement upon proper notice to the other party. Cowen and we each have the right, by giving written notice as specified in the sales agreement, to terminate the sales agreement in each party’s sole discretion at any time.

Pursuant to the sales agreement, the aggregate compensation payable to Cowen as sales agent up to 3.0% of the gross sales price of the shares sold through it pursuant to the sales agreement. We have also agreed to reimburse Cowen up to \$75,000 of Cowen’s actual outside legal expenses incurred by Cowen in connection with this offering, and for certain other expenses. We estimate that the total expenses of the offering payable by us, excluding commissions payable to Cowen under the sales agreement, will be approximately \$325,000.

The remaining sales proceeds, after deducting any expenses payable by us and any transaction fees imposed by any governmental, regulatory, or self-regulatory organization in connection with the sales, will equal our net proceeds for the sale of such common stock.

Cowen will provide written confirmation to us following the close of trading on The Nasdaq Global Select Market on each day in which common stock is sold through it as sales agent under the sales agreement. Each confirmation will include the number of shares of common stock sold through it as sales agent on that day, the volume weighted average price of the shares sold, the percentage of the daily trading volume and the net proceeds to us.

We will report at least quarterly the number of shares of common stock sold through Cowen under the sales agreement, the net proceeds to us and the compensation paid by us to Cowen in connection with the sales of common stock.

Settlement for sales of common stock will occur, unless the parties agree otherwise or as otherwise required by law, on the second business day that is also a trading day following the date on which any sales were made in return for payment of the net proceeds to us. There is no arrangement for funds to be received in an escrow, trust or similar arrangement.

In connection with the sales of our common stock on our behalf, Cowen will be deemed to be an “underwriter” within the meaning of the Securities Act, and the compensation paid to Cowen will be deemed to be underwriting commissions or discounts. We have agreed in the sales agreement to provide indemnification and contribution to

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Cowen against certain liabilities, including liabilities under the Securities Act or the Exchange Act. As sales agent, Cowen will not engage in any transactions that stabilize our common stock.

Our common stock is listed on The Nasdaq Global Select Market and trades under the symbol "SYRS." The transfer agent of our common stock is Computershare Trust Company, N.A.

Cowen and/or its affiliates have provided, and may in the future provide, various investment banking and other financial services for us for which services they have received and, may in the future receive, customary fees.

LEGAL MATTERS

Certain legal matters in connection with this offering will be passed upon for us by Wilmer Cutler Pickering Hale and Dorr LLP, Boston, Massachusetts. Cowen and Company, LLC is being represented by Cooley LLP, New York, New York in connection with this offering.

EXPERTS

The consolidated financial statements of Syros Pharmaceuticals, Inc. appearing in Syros Pharmaceuticals, Inc.'s Annual Report (Form 10-K) for the year ended December 31, 2022, have been audited by Ernst & Young LLP, independent registered public accounting firm, as set forth in their report thereon included therein and incorporated herein by reference. Such financial statements are, and audited financial statements to be included in subsequently filed documents will be, incorporated herein in reliance upon the report of Ernst & Young LLP pertaining to such financial statements (to the extent covered by consents filed with the Securities and Exchange Commission) given on the authority of such firm as experts in accounting and auditing.

\$50,000,000



Common Stock

PROSPECTUS

TD Cowen

April 28, 2023
