

PROSPECTUS

**\$34,000,000**

**Spero Therapeutics, Inc.**

**Common Stock**

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This prospectus provides updated information regarding sales of our common stock pursuant to our “at-the-market offering” program, as described in our original prospectus dated December 11, 2018. In December 2018, we entered into a sales agreement with Cantor Fitzgerald & Co., or Cantor, relating to the sale of shares of our common stock, from time to time, pursuant to “at-the-market offering” as defined in Rule 415 promulgated under the Securities Act of 1933, as amended, or the Securities Act. In accordance with the terms of the sales agreement, we may offer and sell shares of our common stock, par value \$0.001 per share, having an aggregate offering price of up to \$50,000,000 from time to time through Cantor acting as our agent. We call this our “ATM program”. On September 9, 2020, we terminated the original prospectus relating to the ATM program without terminating the underlying sales agreement. As of that date, we had sold approximately \$15.4 million of our common stock pursuant to the ATM program, prior to deducting sales commissions. We are now providing this updated prospectus for potential future use of the remaining ATM program. The remaining amount of shares of common stock which we may sell, from time to time depending on market conditions, pursuant to the sales agreement is up to \$34.0 million as stated above.

Our common stock is listed on The Nasdaq Global Select Market under the symbol “SPRO.” On November 6, 2020, the last reported sale price of our common stock was \$13.68 per share.

The actual amount of any shares to be sold pursuant to the ATM program is at our discretion and dependent on market conditions. Cantor is not required to sell any specific amount of securities, but will act as our sales agent using commercially reasonable efforts to sell on our behalf all of the shares of common stock requested to be sold by us, consistent with its normal trading and sales practices, on mutually agreed terms between Cantor and us. There is no arrangement for funds to be received in any escrow, trust or similar arrangement.

The compensation to Cantor for sales of common stock sold pursuant to the sales agreement will be an amount equal to 3.0% of the gross proceeds of any shares of common stock sold under the sales agreement. In connection with the sale of the common stock on our behalf, Cantor will be deemed to be an “underwriter” within the meaning of the Securities Act and the compensation of Cantor will be deemed to be underwriting commissions or discounts. We have also agreed to provide indemnification and contribution to Cantor with respect to certain liabilities, including liabilities under the Securities Act or the Exchange Act of 1934, as amended, or the Exchange Act.

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**Investing in our common stock involves a high degree of risk. Before making an investment decision, please read the risks described under the caption “[Risk Factors](#)” beginning on page SA-4 of this prospectus and in the documents incorporated by reference into this prospectus.**

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

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The date of this prospectus is November 13, 2020

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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 this shelf registration process, we may from time to time sell shares of our common stock having an aggregate offering price of up to \$34.0 million at prices and on terms to be determined by market conditions at the time of the offering. On September 9, 2020, we terminated the original prospectus relating to the ATM program without terminating the underlying sales agreement. As of that date, we had sold approximately \$15.4 million of our common stock pursuant to the ATM program, prior to deducting sales commissions. We are now providing this updated prospectus for potential future use of the remaining ATM program. The remaining amount of shares of common stock which we may sell, from time to time depending on market conditions, pursuant to the sales agreement is up to \$34.0 million as stated on the cover page of this prospectus.

Before buying any of the common stock that we are offering, we urge you to carefully read this prospectus and all of the information incorporated by reference herein and therein, as well as the additional information described under the headings “Where You Can Find More Information” and “Incorporation of Documents by Reference.” These documents contain important information that you should consider when making your investment decision.

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 in 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 in this prospectus—the statement in the document having the later date modifies or supersedes the earlier statement.

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

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 in this prospectus were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

Unless the context otherwise requires, “Spero,” “SPRO,” “the Company,” “we,” “us,” “our” and similar terms refer to Spero Therapeutics, Inc. and our subsidiaries.

## PROSPECTUS SUMMARY

*The following is a summary of what we believe to be the most important aspects of our business and the offering of our securities under this prospectus. We urge you to read this entire prospectus, including the more detailed consolidated financial statements, notes to the consolidated financial statements and other information incorporated by reference from our other filings with the SEC. Investing in our securities involves risks. Therefore, carefully consider the risk factors set forth herein and in our most recent annual and quarterly filings with the SEC, as well as other information in this prospectus and the documents incorporated by reference herein or therein, before purchasing our securities. Each of the risk factors could adversely affect our business, operating results and financial condition, as well as adversely affect the value of an investment in our securities.*

### ***About Spero Therapeutics, Inc.***

We are a multi-asset, clinical-stage biopharmaceutical company focused on identifying, developing and commercializing treatments in high unmet need areas involving multi-drug resistant, or MDR, bacterial infections and rare diseases. Our most advanced product candidate, Tebipenem Pivoxil Hydrobromide, or tebipenem HBr (previously SPR994), is designed to be the first oral carbapenem-class antibiotic for use in adults to treat MDR Gram-negative infections. Treatment with effective orally administrable antibiotics may prevent hospitalizations for serious infections and enable earlier, more convenient and cost-effective treatment of patients after hospitalization. We are also developing SPR720, a novel oral antibiotic designed for the treatment of a rare, orphan disease caused by pulmonary non-tuberculous mycobacterial infections, or NTM disease. In addition, we have a platform technology known as our Potentiator Platform, which includes an IV-administered product candidate, SPR206, being developed to treat MDR Gram-negative infections in the hospital. We believe that our novel product candidates, if successfully developed and approved, would have a meaningful patient impact and significant commercial applications for the treatment of MDR infections in both the community and hospital settings.

### ***Additional Information***

For additional information related to our business and operations, please refer to the reports incorporated herein by reference, as described under the caption “Incorporation of Documents by Reference” on page SA-22 of this prospectus.

### ***Company History and Our Corporate Information***

We were formed as Spero Therapeutics, LLC in December 2013 under the laws of the State of Delaware. On June 30, 2017, through a series of transactions, Spero Therapeutics, LLC merged with and into Spero Therapeutics, Inc. (formerly known as Spero OpCo, Inc.), a Delaware corporation.

Our principal executive offices are located at 675 Massachusetts Avenue, Cambridge, Massachusetts 02139, and our telephone number is (857) 242-1600. Our website address is [www.sperotherapeutics.com](http://www.sperotherapeutics.com). The information contained on, or that can be accessed through, our website is not part of this prospectus. Investors should not rely on any such information in deciding whether to purchase our securities.

The mark “Spero Therapeutics” is our common law trademark. All other service marks, trademarks and trade names appearing in this prospectus are the property of their respective owners. We do not intend our use or display of other companies’ trade names, trademarks or service marks to imply a relationship with, or an endorsement or sponsorship of us by, these other companies. Solely for convenience, trademarks and tradenames referred to in this prospectus may appear without the ® or TM symbols, but such references are not intended to indicate in any way that we will not assert, to the fullest extent under applicable law, our rights, or that the applicable owner will not assert its rights, to these trademarks and tradenames.

## THE OFFERING

Common stock offered by us	Shares of our common stock having an aggregate offering price of up to \$34,000,000, which is the remaining amount under our original ATM program.
Common stock to be outstanding after this offering	<p>Up to 28,455,485 shares (as more fully described in the notes following this table), assuming sales of 2,485,380 shares of our common stock in this offering at an offering price of \$13.68 per share, which was the last reported sale price of our common stock on The Nasdaq Global Select Market on November 6, 2020.</p> <p>The actual number of shares issued in connection with this offering will vary depending on how many shares of our common stock we choose to sell and the prices at which such sales occur.</p>
Manner of offering	“At-the-market offering” that may be made from time to time through our sales agent, Cantor. See “Plan of Distribution” on page SA-19 of this prospectus.
Use of proceeds	We currently intend to use the net proceeds from this offering for general corporate purposes, including, but not limited to, clinical trials, research and development activities, working capital, capital expenditures, investments, acquisitions, should we choose to pursue any, and collaborations. See the section entitled “Use of Proceeds” on page SA-8 of this prospectus.
Risk factors	See “Risk Factors” beginning on page SA-4 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	“SPRO”

The number of shares of common stock shown above to be outstanding after this offering is based on 25,970,105 shares of our common stock issued and outstanding as of September 30, 2020, and excludes, as of that date:

- 1,720,000 shares of common stock issuable upon conversion of 1,720 shares of our Series A Convertible Preferred Stock as of September 30, 2020;
- 1,000,000 shares of common stock issuable upon conversion of 1,000 shares of our Series B Convertible Preferred Stock as of September 30, 2020;
- 2,287,000 shares of common stock issuable upon conversion of 2,287 shares of our Series C Convertible Preferred Stock as of September 30, 2020;
- 3,215,000 shares of common stock issuable upon conversion of 3,215,000 shares of our Series D Convertible Preferred Stock as of September 30, 2020;
- 1,200,000 shares of common stock issued subsequent to September 30, 2020 pursuant to the exercise of the option to purchase additional shares under the Underwriting Agreement entered into by us on September 10, 2020 in connection with our underwritten public offering completed in September 2020;
- 3,679,383 shares of common stock issuable upon exercise of outstanding options as of September 30, 2020, having a weighted average exercise price of \$8.59 per share, of which 1,776,731 shares were vested as of such date;
- 30,561 shares of common stock issuable upon the vesting and release of outstanding restricted units as of September 30, 2020; and
- 935,501 shares of common stock reserved for future issuance as of September 30, 2020 under our 2017 Stock Incentive Plan, as amended, and under our 2019 Inducement Equity Incentive Plan, as amended.

## 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 described below and discussed under the sections captioned "Risk Factors" contained in our most recent Annual Report on Form 10-K, as well as in any of our subsequent Quarterly Reports on Form 10-Q or our Current Reports on Form 8-K, 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 free writing prospectus that we have authorized 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 be seriously harmed. This could cause the trading price of our common stock to decline, resulting in a loss of all or part of your investment.*

*Our business, financial condition or results of operations could be materially adversely affected by any of these risks. The trading price of our securities could decline due to any of these risks, and you may lose part or all of your investment. This prospectus and the incorporated documents also contain forward-looking statements that involve risks and uncertainties. Our actual results could differ materially from those anticipated in these forward-looking statements as a result of certain factors, including the risks mentioned below. Forward-looking statements included in this prospectus are based on information available to us on the date hereof and all forward-looking statements in documents incorporated by reference are based on information available to us as of the date of such documents. We disclaim any intent to update any forward-looking statements.*

### **Risks Related to This Offering**

***Our management will have broad discretion over the use of the net proceeds from this offering, and you may not agree with how we use the proceeds and the proceeds may not be invested successfully.***

Our management will have broad discretion as to the use of the net proceeds from this offering and could use them for purposes other than those contemplated at the time of this offering. Accordingly, you are relying on the judgment of our management with regard to the use of these net proceeds, and you will not have the opportunity, as part of your investment decision, to assess whether the proceeds will be used appropriately. It is possible that the proceeds will be invested in a way that does not yield a favorable, or any, return for Spero.

***Purchasers may experience immediate dilution in the book value per share of the common stock purchased in the offering.***

The shares sold in this offering, if any, will be sold from time to time at various prices. However, we expect that the offering price of our common stock will be substantially higher than the net tangible book value per share of our outstanding common stock. After giving effect to the assumed sale of shares of our common stock in the aggregate amount of \$34,000,000 at an assumed offering price of \$13.68 per share, the last reported sale price of our common stock on November 6, 2020 on The Nasdaq Global Select Market, and after deducting commissions and estimated offering expenses, our adjusted net tangible book value as of September 30, 2020 would have been approximately \$165.6 million or approximately \$5.82 per share. This would represent an immediate increase in net tangible book value of approximately \$0.71 per share to our existing stockholders and an immediate dilution in adjusted net tangible book value of approximately \$7.86 per share to purchasers of our common stock in this offering.

In addition to this offering, subject to market conditions and other factors, we may pursue additional equity financings in the future, including future public offerings or future private placements of equity securities or securities convertible into or exchangeable for equity securities. Further, the exercise of outstanding stock options or the exercise of stock options issued in the future could result in further dilution to investors and any additional shares issued in connection with acquisitions, should we choose to pursue any, will result in dilution to investors. In addition, the market price of our common stock could fall as a result of resales of any of these shares of common stock due to an increased number of shares available for sale in the market.

***Our stock price is and may continue to be volatile and you may not be able to resell our securities at or above the price you paid.***

The market price for our common stock is volatile and may fluctuate significantly in response to a number of factors, most of which we cannot control, such as quarterly fluctuations in financial results, the timing and our ability to advance the development of our product candidates or changes in securities analysts' recommendations could cause the price of our stock to fluctuate substantially. Each of these factors, among others, could harm your investment in our common stock and could result in your being unable to resell the common stock that you purchase at a price equal to or above the price you paid.

***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 could depress the market price of our common stock and impair our ability to raise capital through the sale of additional equity securities. We cannot predict the effect that future sales of our common stock would have on the market price of our common stock.

## SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents 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 that relate to future events or our future financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to differ materially from any future results, levels of activity, performance or achievements expressed or implied by these forward-looking statements. Words such as, but not limited to, “believe,” “expect,” “anticipate,” “estimate,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “targets,” “likely,” “will,” “would,” “could,” “should,” “continue,” and similar expressions or phrases, or the negative of those expressions or phrases, are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Although we believe that we have a reasonable basis for each forward-looking statement contained in this prospectus and incorporated by reference in this prospectus, we caution you that these statements are based on our projections of the future that are subject to known and unknown risks and uncertainties and other factors that may cause our actual results, level of activity, performance or achievements expressed or implied by these forward-looking statements, to differ. The sections in our periodic reports, including our most recent Annual Report on Form 10-K, as revised or supplemented by our subsequent Quarterly Reports on Form 10-Q or our Current Reports on Form 8-K, entitled “Business,” “Risk Factors,” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” as well as other sections in this prospectus and the other documents or reports incorporated by reference in this prospectus, discuss some of the factors that could contribute to these differences. These forward-looking statements include, among other things, statements about:

- our use of the net proceeds from this offering and our cash runway;
- the timing and outcome of the New Drug Application approval process for tebipenem HBr;
- the initiation, timing, progress and results of, including interim data from, our preclinical studies and clinical trials, and our research and development programs;
- our ability to retain the continued service of our key professionals and to identify, hire and retain additional qualified professionals;
- our ability to advance product candidates into, and successfully complete, clinical trials;
- the timing or likelihood of regulatory filings and approvals;
- the direct and indirect impact of the pandemic caused by an outbreak of a new strain of coronavirus (COVID-19) on our business and operations, including manufacturing, research and development costs, clinical trials, regulatory processes and employee expenses;
- the commercialization of our product candidates, if approved;
- the pricing, coverage and reimbursement of our product candidates, if approved;
- the implementation of our business model, strategic plans for our business and product candidates and our Potentiator Platform;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates and our Potentiator Platform;
- our ability to enter into strategic arrangements and/or collaborations and the potential benefits of such arrangements;
- our estimates regarding expenses, capital requirements and needs for additional financing;
- our financial performance; and
- developments relating to our competitors and our industry.

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. We have included important cautionary statements in this prospectus and in the documents incorporated by reference in this prospectus, particularly in the “Risk Factors” section, that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. For a summary of such factors, please refer to the section entitled “Risk Factors” in this prospectus, as updated and supplemented by the discussion of risks and uncertainties under “Risk Factors” contained in any supplements to

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this prospectus and in our most recent Annual Report on Form 10-K, as revised or supplemented by our subsequent Quarterly Reports on Form 10-Q or our Current Reports on Form 8-K, as well as any amendments thereto, as filed with the SEC and which are incorporated herein by reference. The information contained in this document is believed to be current as of the date of this document. We do not intend to update any of the forward-looking statements after the date of this document to conform these statements to actual results or to changes in our expectations, except as required by law.

In light of these assumptions, risks and uncertainties, the results and events discussed in the forward-looking statements contained in this prospectus or in any document incorporated herein by reference might not occur. Investors are cautioned not to place undue reliance on the forward-looking statements, which speak only as of the date of this prospectus or the date of the document incorporated by reference in this prospectus. We are not under any obligation, and we expressly disclaim any obligation, to update or alter any forward-looking statements, whether as a result of new information, future events or otherwise. All subsequent forward-looking statements attributable to us or to any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to in this section.

## USE OF PROCEEDS

We may issue and sell shares of our common stock having aggregate sale proceeds of up to \$34,000,000 from time to time. Because there is no minimum offering amount required to be sold in connection with 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 any net proceeds from the sale of common stock under this prospectus for general corporate purposes, including, but not limited to, clinical trials, research and development activities, working capital, capital expenditures, investments, acquisitions, should we choose to pursue any, and collaborations. The amounts and timing of our actual expenditures will depend on numerous factors, including the progress of our clinical trials and other development efforts and other factors described under “Risk Factors” in this prospectus and the documents incorporated by reference herein, as well as the amount of cash used in our operations. As a result, our management will have broad discretion to allocate the net proceeds, if any, we receive in connection with securities offered pursuant to this prospectus for any purpose.

## DILUTION

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

As of September 30, 2020, our net tangible book value was \$132.8 million, or \$5.11 per share of common stock. Net tangible book value per share represents the amount of our total tangible assets less total liabilities, divided by 25,970,105, the number of shares of common stock outstanding as of September 30, 2020.

After giving effect to the assumed sale of our common stock in the aggregate amount of \$34,000,000 at an assumed offering price of \$13.68 per share, the last reported sale price of our common stock on The Nasdaq Global Select Market on November 6, 2020, and after deducting commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of September 30, 2020 would have been \$165.6 million, or \$5.82 per share of common stock. This amount would represent an immediate increase in net tangible book value of \$0.71 per share to our existing stockholders and an immediate dilution in net tangible book value of approximately \$7.86 per share to new investors in this offering.

The following table illustrates this calculation on a per share basis. The as adjusted information is illustrative only and will adjust based on the actual price to the public, the actual number of shares sold and other terms of the offering determined at the time shares of our common stock are sold pursuant to this prospectus. The shares sold in this offering, if any, will be sold from time to time at various prices.

Assumed offering price per share	\$13.68
Net tangible book value per share as of September 30, 2020	\$5.11
Increase in net tangible book value per share attributable to this offering	\$0.71
As adjusted net tangible book value per share after this offering	<u>\$5.82</u>
Dilution per share to new investors participating in this offering	<u>\$7.86</u>

The table above assumes for illustrative purposes that an aggregate of 2,485,380 shares of our common stock are sold pursuant to this prospectus at a price of \$13.68 per share, the last reported sale price of our common stock on The Nasdaq Global Select Market on November 6, 2020, for aggregate gross proceeds of \$34.0 million. The shares are being sold from time to time at various prices pursuant to the sales agreement with Cantor. A \$1.00 increase in the assumed offering price of \$13.68 per share, which was the last reported sale price of our common stock on The Nasdaq Global Select Market on November 6, 2020, would increase dilution per share to purchasers by approximately \$0.97, after deducting commissions and estimated offering expenses payable by us. A \$1.00 decrease in the assumed offering price of \$13.68 per share would decrease dilution per share to purchasers by approximately \$0.96, after deducting commissions and estimated offering expenses payable by us.

The above discussion and table are based on 25,970,105 shares of our common stock issued and outstanding as of September 30, 2020, and excludes, as of that date:

- 2,220,000 shares of common stock issuable upon conversion of outstanding shares of our Series A Convertible Preferred Stock as of September 30, 2020;
- 1,000,000 shares of common stock issuable upon conversion of outstanding shares of our Series B Convertible Preferred Stock as of September 30, 2020;
- 2,287,000 shares of common stock issuable upon conversion of outstanding shares of our Series C Convertible Preferred Stock as of September 30, 2020;
- 3,215,000 shares of common stock issuable upon conversion of outstanding shares of our Series D Convertible Preferred Stock as of September 30, 2020;
- 1,200,000 shares of common stock issued subsequent to September 30, 2020 pursuant to the exercise of the option to purchase additional shares under the Underwriting Agreement entered into by us on September 10, 2020 in connection with our underwritten public offering completed in September 2020;

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- 3,679,383 shares of common stock issuable upon exercise of outstanding options as of September 30, 2020, having a weighted average exercise price of \$8.59 per share, of which 1,776,731 shares were vested as of such date;
- 30,561 shares of common stock issuable upon the vesting and release of outstanding restricted units as of September 30, 2020; and
- 935,501 shares of common stock reserved for future issuance as of September 30, 2020 under our 2017 Stock Incentive Plan, as amended, and under our 2019 Inducement Equity Incentive Plan, as amended.

To the extent that outstanding options are exercised or outstanding shares of our preferred stock are converted into shares of our common stock, you will experience further dilution. In addition, we may choose to raise additional capital due to market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of these securities may result in further dilution to our stockholders.

## DESCRIPTION OF CAPITAL STOCK

We are authorized to issue 60,000,000 shares of common stock, par value \$0.001 per share, and 10,000,000 shares of preferred stock, par value \$0.001 per share. As of November 6, 2020, we had 27,196,996 shares of common stock outstanding held by approximately 10 stockholders of record, and 3,220,007 shares of preferred stock outstanding held by four stockholders of record all of which preferred stockholders of record are affiliates of BVF Partners, L.P. Subject to the blocker provisions and other terms described below, the aggregate amount of shares of preferred stock outstanding as of November 6, 2020 would be convertible into an aggregate of 8,222,000 shares of common stock.

The following summary of certain provisions of our capital stock does not purport to be complete. You should refer to the section of this prospectus entitled “Certain Provisions of Delaware Law and of the Company’s Certificate of Incorporation and Bylaws” and our amended and restated certificate of incorporation and our amended and restated bylaws, both of which are included as exhibits to the registration statement of which this prospectus is a part. The summary below is also qualified by provisions of applicable law.

### **Common Stock**

#### ***General***

We are authorized to issue one class of common stock. Holders of our common stock are entitled to one vote for each share of common stock held of record for the election of directors and on all matters submitted to a vote of stockholders. Holders of our common stock are entitled to receive dividends ratably, if any, as may be declared by our board of directors out of legally available funds, subject to any preferential dividend rights of any preferred stock then outstanding. Upon our dissolution, liquidation or winding up, holders of our common stock are entitled to share ratably in our net assets legally available after the payment of all our debts and other liabilities, subject to the preferential rights of any preferred stock then outstanding. Holders of our common stock have no preemptive, subscription, redemption or conversion rights. The rights, preferences and privileges of holders of common stock are subject to, and may be adversely affected by, the rights of the holders of shares of any series of preferred stock that are currently designated and issued or that we may designate and issue in the future. Except as described under “Certain Provisions of Delaware Law and of the Company’s Certificate of Incorporation and Bylaws—Anti-Takeover Provisions” below, a majority vote of the holders of common stock is generally required to take action under our amended and restated certificate of incorporation and amended and restated bylaws.

#### ***Transfer Agent and Registrar***

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

#### ***Stock Exchange Listing***

Our common stock is listed for quotation on The Nasdaq Global Select Market under the symbol “SPRO.”

#### ***Preferred Stock***

Our board of directors is authorized, without action by the stockholders, to designate and issue up to an aggregate of 10,000,000 shares of preferred stock in one or more series. Our board of directors can designate the rights, preferences and privileges of the shares of each series and any of its qualifications, limitations or restrictions. Our board of directors may authorize the issuance of preferred stock with voting or conversion rights that could adversely affect the voting power or other rights of the holders of common stock. The issuance of preferred stock, while providing flexibility in connection with possible future financings and acquisitions and other corporate purposes could, under certain circumstances, have the effect of restricting dividends on our common stock, diluting the voting power of our common stock, impairing the liquidation rights of our common stock, or delaying, deferring or preventing a change in control of our company, which might harm the market price of our common stock. See also “Certain Provisions of Delaware Law and of the Company’s Certificate of Incorporation and Bylaws—Anti-Takeover Provisions.” Our board of directors will make any determination to issue such shares based on its judgment as to our company’s best interests and the best interests of our stockholders.

### ***Series A Preferred Stock***

*General.* Our board of directors has designated 2,220 of the 10,000,000 authorized shares of preferred stock as Series A Convertible Preferred Stock, or the Series A Preferred Stock.

*Rank.* The shares of Series A Preferred Stock rank:

- senior to all of our common stock;
- senior to any class or series of our capital stock hereafter created specifically ranking by its terms junior to the Series A Preferred Stock;
- on parity to any class or series of our capital stock hereafter created specifically ranking by its terms on parity with the Series A Preferred Stock; and
- junior to any class or series of our capital stock hereafter created specifically ranking by its terms senior to the Series A Preferred Stock;

in each case, as to distributions of assets upon our liquidation, dissolution or winding up whether voluntarily or involuntarily and/or the right to receive dividends.

*Conversion.* Each share of the Series A Preferred Stock is convertible into 1,000 shares of our common stock (subject to adjustment as provided in the certificate of designation for our Series A Preferred Stock, or the Series A Certificate of Designation) at any time at the option of the holder, provided that the holder is prohibited from converting Series A Preferred Stock into shares of our common stock if, as a result of such conversion, the holder, together with its affiliates and any other persons whose beneficial ownership of our common stock would be aggregated with such holder's for purposes of Section 13(d) or Section 16 of the Exchange Act, and the applicable regulations of the SEC, would own more than 9.99% of the total number of shares of our common stock then issued and outstanding. The holder of such shares of Series A Preferred Stock can, upon 61 days' notice to us, change this requirement to a higher or lower percentage, not to exceed 9.99% of the number of shares of our common stock outstanding immediately after giving effect to such conversion. At any time following notice of a Fundamental Transaction (as defined in the Series A Certificate of Designation), the holder of such shares of Series A Preferred Stock may waive and/or change the 9.99% ownership limitation effective immediately upon written notice to us.

*Liquidation Preference.* Each holder of shares of Series A Preferred Stock is entitled to receive, in preference to any distributions of any of the assets or surplus funds of the Company to the holders of our common stock and any of our securities that by their terms are junior to the Series A Preferred Stock and *pari passu* with any distribution to the holders of any securities having (by their terms) parity with the Series A Preferred Stock, an amount equal to \$0.001 per share of Series A Preferred Stock, plus an additional amount equal to any dividends declared but unpaid on such shares, before any payments shall be made or any assets distributed to holders of any class of common stock or securities that by their terms are junior to the Series A Preferred Stock. If, upon any such liquidation, dissolution or winding up of the Company, the assets of the Company shall be insufficient to pay the holders of shares of the Series A Preferred Stock the amount required under the preceding sentence, then all remaining assets of the Company shall be distributed ratably to holders of the shares of the Series A Preferred Stock and any securities having (by their terms) parity with the Series A Preferred Stock. After such preferential payment, each holder of shares of Series A Preferred Stock shall be entitled to participate *par/ passu* with the holders of common stock (on an as-converted basis, without regard to the 9.99% beneficial ownership limitation) and any securities having (by their terms) parity with the Series A Preferred Stock in the remaining distribution of the net assets of the Company available for distribution.

*Voting Rights.* Shares of Series A Preferred Stock generally have no voting rights, except as required by law and except that the consent of the holders of the outstanding Series A Preferred Stock is required to amend the terms of the Series A Preferred Stock.

*Dividends.* Shares of Series A Preferred Stock are entitled to receive any dividends payable to holders of our common stock.

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*Redemption.* We are not obligated to redeem or repurchase any shares of Series A Preferred Stock. Shares of Series A Preferred Stock are not entitled to any redemption rights or mandatory sinking fund or analogous fund provisions.

*Listing.* Our Series A Preferred Stock is not currently listed on any securities exchange or other trading system. We expect the common stock issuable upon conversion of the Series A Preferred Stock to be listed on The Nasdaq Global Select Market.

### **Series B Preferred Stock**

*General.* Our board of directors has designated 1,000 of the 10,000,000 authorized shares of preferred stock as Series B Convertible Preferred Stock, or the Series B Preferred Stock.

*Rank.* The shares of Series B Preferred Stock rank:

- senior to all of our common stock;
- senior to any class or series of our capital stock hereafter created specifically ranking by its terms junior to the Series B Preferred Stock;
- on parity to all our shares of Series A Preferred Stock;
- on parity to any class or series of our capital stock hereafter created specifically ranking by its terms on parity with the Series B Preferred Stock; and
- junior to any class or series of our capital stock hereafter created specifically ranking by its terms senior to the Series B Preferred Stock;

in each case, as to distributions of assets upon our liquidation, dissolution or winding up whether voluntarily or involuntarily and/or the right to receive dividends.

*Conversion.* Each share of the Series B Preferred Stock is convertible into 1,000 shares of our common stock (subject to adjustment as provided in the certificate of designation for our Series B Preferred Stock, or the Series B Certificate of Designation) at any time at the option of the holder, provided that the holder is prohibited from converting Series B Preferred Stock into shares of our common stock if, as a result of such conversion, the holder, together with its affiliates and any other persons whose beneficial ownership of our common stock would be aggregated with such holder's for purposes of Section 13(d) or Section 16 of the Exchange Act, and the applicable regulations of the SEC, would own more than 9.99% of the total number of shares of our common stock then issued and outstanding. The holder of such shares of Series B Preferred Stock can, upon 61 days' notice to us, change this requirement to a higher or lower percentage, not to exceed 9.99% of the number of shares of our common stock outstanding immediately after giving effect to such conversion. At any time following notice of a Fundamental Transaction (as defined in the Series B Certificate of Designation), the holder of such shares of Series B Preferred Stock may waive and/or change the 9.99% ownership limitation effective immediately upon written notice to us.

*Liquidation Preference.* Each holder of shares of Series B Preferred Stock is entitled to receive, in preference to any distributions of any of the assets or surplus funds of the Company to the holders of our common stock and any of our securities that by their terms are junior to the Series B Preferred Stock and *pari passu* with any distribution to the holders of any securities having (by their terms) parity with the Series B Preferred Stock, including the Series A Preferred Stock, an amount equal to \$0.001 per share of Series B Preferred Stock, plus an additional amount equal to any dividends declared but unpaid on such shares, before any payments shall be made or any assets distributed to holders of any class of common stock or any of our securities that by their terms are junior to the Series B Preferred Stock. If, upon any such liquidation, dissolution or winding up of the Company, the assets of the Company shall be insufficient to pay the holders of shares of the Series B Preferred Stock the amount required under the preceding sentence, then all remaining assets of the Company shall be distributed ratably to holders of the shares of the Series B Preferred Stock and any securities having (by their terms) parity with the Series B Preferred Stock, including the Series A Preferred Stock. After such preferential payment, each holder of shares of Series B Preferred Stock shall be entitled to participate *pari passu* with the holders of common stock (on an as-converted basis, without regard to the 9.99% beneficial ownership limitation) and any securities having (by their terms) parity with the Series B Preferred Stock,

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including the Series A Preferred Stock, in the remaining distribution of the net assets of the Company available for distribution.

*Voting Rights.* Shares of Series B Preferred Stock generally have no voting rights, except as required by law and except that the consent of the holders of the outstanding Series B Preferred Stock is required to amend the terms of the Series B Preferred Stock.

*Dividends.* Shares of Series B Preferred Stock are entitled to receive any dividends payable to holders of our common stock.

*Redemption.* We are not obligated to redeem or repurchase any shares of Series B Preferred Stock. Shares of Series B Preferred Stock are not entitled to any redemption rights or mandatory sinking fund or analogous fund provisions.

*Listing.* Our Series B Preferred Stock is not currently listed on any securities exchange or other trading system. We expect the common stock issuable upon conversion of the Series B Preferred Stock to be listed on The Nasdaq Global Select Market.

### **Series C Preferred Stock**

*General.* Our board of directors has designated 3,333 of the 10,000,000 authorized shares of preferred stock as Series C Convertible Preferred Stock, or the Series C Preferred Stock.

*Rank.* The shares of Series C Preferred Stock rank:

- senior to all of our common stock;
- senior to any class or series of our capital stock hereafter created specifically ranking by its terms junior to the Series C Preferred Stock;
- on parity to all our shares of Series A Preferred Stock and Series B Preferred Stock;
- on parity to any class or series of our capital stock hereafter created specifically ranking by its terms on parity with the Series C Preferred Stock; and
- junior to any class or series of our capital stock hereafter created specifically ranking by its terms senior to the Series C Preferred Stock;

in each case, as to distributions of assets upon our liquidation, dissolution or winding up whether voluntarily or involuntarily and/or the right to receive dividends.

*Conversion.* Each share of the Series C Preferred Stock is convertible into 1,000 shares of our common stock (subject to adjustment as provided in the certificate of designation for our Series C Preferred Stock, or the Series C Certificate of Designation) at any time at the option of the holder, provided that the holder is prohibited from converting Series C Preferred Stock into shares of our common stock if, as a result of such conversion, the holder, together with its affiliates and any other persons whose beneficial ownership of our common stock would be aggregated with such holder's for purposes of Section 13(d) or Section 16 of the Exchange Act, and the applicable regulations of the SEC, would own more than 9.99% of the total number of shares of our common stock then issued and outstanding. The holder of such shares of Series C Preferred Stock can, upon 61 days' notice to us, change this requirement to a higher or lower percentage, not to exceed 9.99% of the number of shares of our common stock outstanding immediately after giving effect to such conversion. At any time following notice of a Fundamental Transaction (as defined in the Series C Certificate of Designation), the holder of such shares of Series C Preferred Stock may waive and/or change the 9.99% ownership limitation effective immediately upon written notice to us.

*Liquidation Preference.* Each holder of shares of Series C Preferred Stock is entitled to receive, in preference to any distributions of any of the assets or surplus funds of the Company to the holders of our common stock and any of our securities that by their terms are junior to the Series C Preferred Stock and *pari passu* with any distribution to the holders of any securities having (by their terms) parity with the Series C Preferred Stock, including the Series A Preferred Stock and the Series B Preferred Stock, an amount equal to \$0.001 per share of Series C Preferred Stock, plus an additional amount equal to any dividends declared but

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unpaid on such shares, before any payments shall be made or any assets distributed to holders of any class of common stock or any of our securities that by their terms are junior to the Series C Preferred Stock. If, upon any such liquidation, dissolution or winding up of the Company, the assets of the Company shall be insufficient to pay the holders of shares of the Series C Preferred Stock the amount required under the preceding sentence, then all remaining assets of the Company shall be distributed ratably to holders of the shares of the Series C Preferred Stock and any securities having (by their terms) parity with the Series C Preferred Stock, including the Series A Preferred Stock and Series B Preferred Stock. After such preferential payment, each holder of shares of Series C Preferred Stock shall be entitled to participate *pari passu* with the holders of common stock (on an as-converted basis, without regard to the 9.99% beneficial ownership limitation) and any securities having (by their terms) parity with the Series C Preferred Stock, including the Series A Preferred Stock and Series B Preferred Stock Preferred Stock, in the remaining distribution of the net assets of the Company available for distribution.

*Voting Rights.* Shares of Series C Preferred Stock generally have no voting rights, except as required by law and except that the consent of the holders of the outstanding Series C Preferred Stock is required to amend the terms of the Series C Preferred Stock.

*Dividends.* Shares of Series C Preferred Stock are entitled to receive any dividends payable to holders of our common stock.

*Redemption.* We are not obligated to redeem or repurchase any shares of Series C Preferred Stock. Shares of Series C Preferred Stock are not entitled to any redemption rights or mandatory sinking fund or analogous fund provisions.

*Listing.* Our Series C Preferred Stock is not currently listed on any securities exchange or other trading system. We expect the common stock issuable upon conversion of the Series C Preferred Stock to be listed on The Nasdaq Global Select Market.

### **Series D Preferred Stock**

*General.* Our board of directors has designated 3,215,000 of the 10,000,000 authorized shares of preferred stock as Series D Convertible Preferred Stock, or the Series D Preferred Stock.

*Rank.* The shares of Series D Preferred Stock rank:

- senior to all of our common stock;
- senior to any class or series of our capital stock hereafter created specifically ranking by its terms junior to the Series D Preferred Stock;
- on parity to all our shares of Series A Preferred Stock, Series B Preferred Stock and Series C Preferred Stock;
- on parity to any class or series of our capital stock hereafter created specifically ranking by its terms on parity with the Series D Preferred Stock; and
- junior to any class or series of our capital stock hereafter created specifically ranking by its terms senior to the Series D Preferred Stock;

in each case, as to distributions of assets upon our liquidation, dissolution or winding up whether voluntarily or involuntarily and/or the right to receive dividends.

*Conversion.* The shares of the Series D Preferred Stock are convertible on a one-to-one basis into shares of our common stock (subject to adjustment as provided in the certificate of designation for our Series D Preferred Stock, or the Series D Certificate of Designation) at any time at the option of the holder, provided that the holder is prohibited from converting Series D Preferred Stock into shares of our common stock if, as a result of such conversion, the holder, together with its affiliates and any other persons whose beneficial ownership of our common stock would be aggregated with such holder's for purposes of Section 13(d) or Section 16 of the Exchange Act, and the applicable regulations of the SEC, would own more than 9.99% of the total number of shares of our common stock then issued and outstanding. The holder of such shares of Series D Preferred Stock can, upon 61 days' notice to us, change this requirement to a higher or lower percentage, not to exceed 9.99% of the number of shares of our common stock outstanding immediately after giving effect to such conversion. At

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any time following notice of a Fundamental Transaction (as defined in the Series D Certificate of Designation), the holder of such shares of Series D Preferred Stock may waive and/or change the 9.99% ownership limitation effective immediately upon written notice to us.

*Liquidation Preference.* Each holder of shares of Series D Preferred Stock is entitled to receive, in preference to any distributions of any of the assets or surplus funds of the Company to the holders of our common stock and any of our securities that by their terms are junior to the Series D Preferred Stock and pari passu with any distribution to the holders of any securities having (by their terms) parity with the Series D Preferred Stock, including the Series A Preferred Stock, Series B Preferred Stock and Series C Preferred Stock, an amount equal to \$0.001 per share of Series D Preferred Stock, plus an additional amount equal to any dividends declared but unpaid on such shares, before any payments shall be made or any assets distributed to holders of any class of common stock or any of our securities that by their terms are junior to the Series D Preferred Stock. If, upon any such liquidation, dissolution or winding up of the Company, the assets of the Company shall be insufficient to pay the holders of shares of the Series D Preferred Stock the amount required under the preceding sentence, then all remaining assets of the Company shall be distributed ratably to holders of the shares of the Series D Preferred Stock and any securities having (by their terms) parity with the Series D Preferred Stock, including the Series A Preferred Stock, Series B Preferred Stock and Series C Preferred Stock, in the remaining distribution of the net assets of the Company available for distribution.

*Voting Rights.* Shares of Series D Preferred Stock generally have no voting rights, except as required by law and except that the consent of the holders of the outstanding Series D Preferred Stock is required to amend the terms of the Series D Preferred Stock.

*Dividends.* Shares of Series D Preferred Stock are entitled to receive any dividends payable to holders of our common stock.

*Redemption.* We are not obligated to redeem or repurchase any shares of Series D Preferred Stock. Shares of Series D Preferred Stock are not entitled to any redemption rights or mandatory sinking fund or analogous fund provisions.

*Listing.* Our Series D Preferred Stock is not currently listed on any securities exchange or other trading system. We expect the common stock issuable upon conversion of the Series D Preferred Stock to be listed on The Nasdaq Global Select Market.

### ***Transfer Agent and Registrar***

The transfer agent and registrar for our Series A Preferred Stock, Series B Preferred Stock, Series C Preferred Stock and Series D Preferred Stock is Computershare Trust Company, N.A.

## CERTAIN PROVISIONS OF DELAWARE LAW AND OF THE COMPANY'S CERTIFICATE OF INCORPORATION AND BYLAWS

### Anti-Takeover Provisions

#### *Delaware Law*

We are subject to Section 203 of the Delaware General Corporation Law. 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 the sale of more than 10% of our assets. In general, an "interested stockholder" is any entity or person beneficially owning 15% or more of our outstanding voting stock and any entity or person affiliated with or controlling or controlled by such entity or person.

#### *Charter Documents*

In accordance with our amended and restated certificate of incorporation, our board is divided into three classes serving three-year terms, with one class being elected each year. The provision for a classified board could prevent a party who acquires control of a majority of our outstanding voting stock from obtaining control of the our board of directors until the second annual stockholders meeting following the date the acquirer obtains the controlling stock interest. Our classified board provision could also discourage a potential acquirer from making a tender offer or otherwise attempting to obtain control of Spero and could increase the likelihood that incumbent directors will retain their positions.

Our amended and restated certificate of incorporation also provides that directors may be removed only for cause and then only by the affirmative vote of the holders of 75% or more of the shares then entitled to vote at an election of directors. Furthermore, any vacancy on our board of directors, however occurring, including a vacancy resulting from an increase in the size of our board, may only be filled by the affirmative vote of a majority of our directors then in office, even if less than a quorum.

As required by the Delaware General Corporation Law, any amendment of our amended and restated certificate of incorporation must first be approved by a majority of our board of directors and, if required by law or our amended and restated certificate of incorporation, thereafter be approved by a majority of the outstanding shares entitled to vote on the amendment, and a majority of the outstanding shares of each class entitled to vote thereon as a class, except that the amendment of the provisions relating to stockholder action, directors, limitation of liability, exclusive jurisdiction of Delaware Courts and the amendment of our amended and restated bylaws and amended and restated certificate of incorporation must be approved by not less than 75% of the outstanding shares entitled to vote on the amendment, and not less than 75% of the outstanding shares of each class entitled to vote thereon as a class. Our amended and restated bylaws may be amended by the affirmative vote of a majority of the directors then in office, subject to any limitations set forth in our amended and restated bylaws; and may also be amended by the affirmative vote of at least 75% of the outstanding shares entitled to vote on the amendment, or, if our board of directors recommends that the stockholders approve the amendment, by the affirmative vote of the majority of the outstanding shares entitled to vote on the amendment, in each case voting together as a single class. These provisions could discourage a potential acquirer from making a tender offer or otherwise attempting to obtain control of Spero and could delay changes in management.

Our amended and restated bylaws establish advance notice procedures with regard to stockholder proposals relating to the nomination of candidates for election as directors or new business to be brought before meetings of our stockholders. These procedures provide that notice of stockholder proposals must be timely given in writing to our corporate secretary prior to the meeting at which the action is to be taken. Generally, to be timely, notice must be received at our principal executive offices not less than 90 days or more than 120 days prior to the first anniversary date of the annual meeting for the preceding year. The notice must contain certain information specified in our amended and restated bylaws. These provisions may have the effect of precluding the conduct of

certain business at a meeting if the proper procedures are not followed. These provisions may also discourage or deter a potential acquirer from conducting a solicitation of proxies to elect the acquirer's own slate of directors or otherwise attempting to obtain control of our company.

Our amended and restated bylaws provide that only a majority of the members of our board of directors then in office may call special meetings of stockholders and only those matters set forth in the notice of the special meeting may be considered or acted upon at a special meeting of stockholders. Our amended and restated bylaws limit the business that may be conducted at an annual meeting of stockholders to those matters properly brought before the meeting. The restriction on the ability of our stockholders to call a special meeting means that a proposal to replace one or more directors on our board of directors also could be delayed until the next annual meeting.

Our amended and restated certificate of incorporation also provides that all stockholder actions are required to be taken by a vote of the stockholders at an annual or special meeting, and that stockholders may not take any action by written consent in lieu of a meeting. Without the availability of stockholder action by written consent, a holder controlling a majority of our capital stock would not be able to amend Spero's amended and restated bylaws or remove directors without holding a stockholders' meeting.

#### **Limitation of Liability and Indemnification**

Our amended and restated certificate of incorporation provides that no director of our company shall be personally liable to us or our stockholders for monetary damages for any breach of fiduciary duty as a director, except for liability (1) for any breach of the director's duty of loyalty to us or our stockholders, (2) for acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law, (3) in respect of unlawful dividend payments or stock redemptions or repurchases, or (4) for any transaction from which the director derived an improper personal benefit. In addition, our amended and restated certificate of incorporation provides that if the Delaware General Corporation Law is amended to authorize the further elimination or limitation of the liability of directors, then the liability of a director of our company shall be eliminated or limited to the fullest extent permitted by the Delaware General Corporation Law, as so amended.

Our amended and restated certificate of incorporation further provides that any repeal or modification of such article by our stockholders or amendment to the Delaware General Corporation Law will not adversely affect any right or protection existing at the time of such repeal or modification with respect to any acts or omissions occurring before such repeal or modification of a director serving at the time of such repeal or modification.

Our amended and 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 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 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 amended and restated certificate of incorporation also provides that we will advance expenses to Indemnitees in connection with a legal proceeding, subject to limited exceptions.

We have entered into indemnification agreements with each of our directors and our executive officers. These agreements provide that we will indemnify each of our directors and such officers to the fullest extent permitted by law and by our amended and restated certificate of incorporation and amended and restated bylaws.

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

## PLAN OF DISTRIBUTION

On December 3, 2018, we entered into a Controlled Equity Offering<sup>SM</sup> sales agreement with Cantor under which we may issue and sell shares of our common stock having an aggregate gross sales price of up to \$50,000,000 from time to time through Cantor, acting as agent. The sales agreement was filed as an exhibit to our registration statement on Form S-3 dated December 3, 2018. On September 9, 2020, we terminated the original prospectus relating to the ATM program without terminating the underlying sales agreement. As of that date, we had sold approximately \$15.4 million of our common stock pursuant to the ATM program, prior to deducting sales commissions. We are now providing this updated prospectus for potential future use of the remaining ATM program. The remaining amount of shares of common stock which we may sell, from time to time depending on market conditions, pursuant to the sales agreement is up to \$34.0 million as stated on the cover page of this prospectus.

Upon delivery of a placement notice and subject to the terms and conditions of the sales agreement, Cantor may sell our common stock by any method permitted by law deemed to be an “at-the-market” offering as defined in Rule 415 promulgated under the Securities Act. We may instruct Cantor not to sell common stock if the sales cannot be effected at or above the price designated by us from time to time. We or Cantor may suspend the offering of common stock upon notice and subject to other conditions.

We will pay Cantor commissions, in cash, for its services in acting as agent in the sale of our common stock. Cantor will be entitled to compensation at a fixed commission rate of 3.0% of the gross proceeds from each sale of our common stock. 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 have also agreed to reimburse Cantor for certain specified expenses, including the fees and disbursements of its legal counsel in an amount not to exceed \$50,000. We estimate that the total expenses for the offering, excluding compensation and reimbursements payable to Cantor under the terms of the sales agreement, will be approximately \$175,000.

Settlement for sales of common stock will occur on the second business day following the date on which any sales are made, or on some other date that is agreed upon by us and Cantor in connection with a particular transaction, in return for payment of the net proceeds to us. Sales of our common stock as contemplated in this prospectus will be settled through the facilities of The Depository Trust Company or by such other means as we and Cantor may agree upon. There is no arrangement for funds to be received in an escrow, trust or similar arrangement.

Cantor will use its commercially reasonable efforts, consistent with its sales and trading practices, to solicit offers to purchase the common stock shares under the terms and subject to the conditions set forth in the sales agreement. In connection with the sale of the common stock on our behalf, Cantor will be deemed to be an “underwriter” within the meaning of the Securities Act and the compensation of Cantor will be deemed to be underwriting commissions or discounts. We have agreed to provide indemnification and contribution to Cantor against certain civil liabilities, including liabilities under the Securities Act.

The offering of our common stock pursuant to the sales agreement will terminate upon the termination of the sales agreement as permitted therein. We and Cantor may each terminate the sales agreement at any time upon ten days’ prior notice or by Cantor at any time in certain circumstances, including the occurrence of a material and adverse change in our business or financial condition that makes it impractical or inadvisable to market our common stock or to enforce contracts for the sale of our common stock.

Cantor and its affiliates may in the future provide various investment banking, commercial banking and other financial services for us and our affiliates, for which services they may in the future receive customary fees. To the extent required by Regulation M, Cantor will not engage in any market making activities involving our common stock while the offering is ongoing under this prospectus.

This prospectus in electronic format may be made available on a website maintained by Cantor and Cantor may distribute this prospectus electronically.

**LEGAL MATTERS**

Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., Boston, Massachusetts, will pass upon the validity of the issuance of the securities to be offered by this prospectus. Cantor is being represented by Latham & Watkins LLP, San Diego, California in connection with this offering.

**EXPERTS**

The financial statements incorporated in this prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2019 have been so incorporated in reliance on the report (which contains an explanatory paragraph related to substantial doubt about the Company's ability to continue as a going concern, as described in Note 1 to the consolidated financial statements) of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

## WHERE YOU CAN FIND MORE INFORMATION

We are subject to the reporting requirements of the Exchange Act and file annual, quarterly and current reports, proxy statements and other information with the SEC. SEC filings are available at the SEC's website at <http://www.sec.gov>.

This prospectus is only part of a registration statement on Form S-3 that we have filed with the SEC under the Securities Act and therefore omits certain information contained in the registration statement. We have also filed exhibits and schedules with the registration statement that are excluded from this prospectus, and you should refer to the applicable exhibit or schedule for a complete description of any statement referring to any contract or other document.

We also maintain a website at [www.sperotherapeutics.com](http://www.sperotherapeutics.com) through which you can access our SEC filings. The information set forth on our website is not part of this prospectus.

## INCORPORATION OF DOCUMENTS BY REFERENCE

The SEC allows us to “incorporate by reference” information that we file with them. Incorporation by reference allows us to disclose important information to you by referring you to those other documents. The information incorporated by reference is an important part of this prospectus, and information that we file later with the SEC will automatically update and supersede this information. We filed a registration statement on Form S-3 under the Securities Act with the SEC with respect to the securities we may offer pursuant to this prospectus. This prospectus omits certain information contained in the registration statement, as permitted by the SEC. You should refer to the registration statement, including the exhibits, for further information about us and the securities we may offer pursuant to this prospectus. Statements in this prospectus regarding the provisions of certain documents filed with, or incorporated by reference in, the registration statement are not necessarily complete and each statement is qualified in all respects by that reference. Copies of all or any part of the registration statement, including the documents incorporated by reference or the exhibits, may be obtained upon payment of the prescribed rates at the offices of the SEC listed above in “Where You Can Find More Information.” The documents we are incorporating by reference are:

- our Annual Report on [Form 10-K](#) for the fiscal year ended December 31, 2019, filed with the SEC on March 16, 2020;
- the portions of our [definitive Proxy Statement](#) on Schedule 14A for our 2020 Annual Meeting of Stockholders, filed with the SEC on September 30, 2020 that are deemed “filed” with the SEC under the Exchange Act;
- our Quarterly Reports on Form 10-Q for the fiscal quarters ended [March 31, 2020](#), [June 30, 2020](#) and [September 30, 2020](#), filed with the SEC on May 8, 2020, August 6, 2020 and November 5, 2020, respectively;
- our Current Reports on Form 8-K (and amendments thereto), filed with the SEC on [January 30, 2020](#), [February 11, 2020](#), [February 28, 2020](#), [April 16, 2020](#) (as amended by the Current Report Form 8-K/A filed with the SEC on [May 11, 2020](#)), [June 4, 2020](#), [September 8, 2020](#), [September 9, 2020](#), [September 14, 2020](#) and [October 28, 2020](#) (except for the information furnished under Items 2.02 or 7.01 and the exhibits furnished thereto);
- the description of our common stock contained in our Registration Statement on [Form 8-A](#) initially filed on October 30, 2017, including any amendment or report filed for the purpose of updating such description; and
- all reports and other documents subsequently filed by us pursuant to Sections 13(a), 13(c), 14 and 15(d) of the Exchange Act after the date of this prospectus and prior to the termination or completion of the offering of securities under this prospectus shall be deemed to be incorporated by reference in this prospectus and to be a part hereof from the date of filing such reports and other documents.

The SEC file number for each of the documents listed above is 001-38266.

Any statement contained in this prospectus or in a document incorporated or deemed to be incorporated by reference into this prospectus will be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus or any other subsequently filed document that is deemed to be incorporated by reference into this prospectus modifies or supersedes the statement. Any statement so modified or superseded will not be deemed, except as so modified or superseded, to constitute a part of this prospectus.

You may request, orally or in writing, a copy of any or all of the documents incorporated herein by reference. These documents will be provided to you at no cost, by contacting:

Spero Therapeutics, Inc.  
675 Massachusetts Avenue, 14th Floor  
Cambridge, Massachusetts 02139  
Telephone: (857) 242-1600

You may also access these documents on our website, <http://www.sperotherapeutics.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.

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You should rely only on information contained in, or incorporated by reference into, this prospectus. We have not authorized anyone to provide you with information different from that contained in this prospectus or incorporated by reference in this prospectus. We are not making offers to sell the securities in any jurisdiction in which such an offer or solicitation is not authorized or in which the person making such offer or solicitation is not qualified to do so or to anyone to whom it is unlawful to make such offer or solicitation.

**\$34,000,000**

**Spero Therapeutics, Inc.**

**Common Stock**

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**PROSPECTUS**

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**November 13, 2020**

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