

PROSPECTUS SUPPLEMENT
(to the Prospectus dated December 3, 2018)

Up to \$10,000,000



Common Stock

Pursuant to this prospectus supplement and the accompanying prospectus, we are offering up to an aggregate of \$10,000,000 of our common stock, \$0.001 par value per share, in up to two closings. In the initial closing, we are offering 465,983 shares of our common stock at an offering price of \$10.73 per share directly to an investor pursuant to a securities purchase agreement between us and such investor dated June 12, 2019, or the Purchase Agreement. The total gross proceeds to us from the initial closing, before expenses, will be approximately \$5,000,000.

As further described in this prospectus supplement, in the second closing, we will sell up to an additional \$5,000,000 of our common stock to such investor pursuant to the Purchase Agreement at a price per share equal to the volume weighted average price of our common stock for the ten consecutive trading days immediately preceding the date of the second closing. The date of the second closing will be the earlier of (i) the eleventh trading day immediately following the date of our public announcement of pharmacokinetic data from the lead-in cohort in our pivotal Phase 3 clinical trial of SPR994, or the SPR994 Data Disclosure Date, or (ii) June 30, 2020, subject to the satisfaction of certain conditions set forth in the Purchase Agreement. Pursuant to the Purchase Agreement, the investor shall have no obligation to purchase shares of our common stock in the second closing, and the second closing shall not occur, if, prior to and continuing as of the SPR994 Data Disclosure Date, we shall have ceased all research and development (including clinical development) of SPR720.

This offering is being made without a placement agent, underwriter, broker or dealer. We are not paying underwriting discounts or commissions in connection with this offering.

Our common stock is traded on The Nasdaq Global Select Market under the symbol "SPRO". The last reported sales price of our common stock on The Nasdaq Global Select Market on June 11, 2019 was \$10.25 per share.

Investing in our common stock involves a high degree of risk. You should review carefully the risks and uncertainties referenced under the heading "[Risk Factors](#)" on page S-5 of this prospectus supplement and in the documents that are incorporated by reference into this prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus supplement is truthful or complete. Any representation to the contrary is a criminal offense.

Delivery of the shares of common stock to be issued in the initial closing is expected to be made on or about June 14, 2019, subject to the satisfaction of certain conditions set forth in the Purchase Agreement.

The date of this prospectus supplement is June 12, 2019.

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ABOUT THIS PROSPECTUS SUPPLEMENT

This prospectus supplement and the accompanying prospectus form part of a registration statement on Form S-3 that we filed with the Securities and Exchange Commission, or SEC, utilizing a “shelf” registration process. Under the shelf registration process, we may from time to time offer and sell any combination of the securities described in the accompanying prospectus up to a total dollar amount of \$200.0 million, of which this offering is a part.

Unless the context otherwise indicates, references in this prospectus to “Spero”, “we”, “our”, “us” and “the Company” refer, collectively, to Spero Therapeutics, Inc., a Delaware corporation, together with its subsidiaries.

This document is in two parts. The first part is this prospectus supplement, which describes the terms of this offering of our common stock and also adds to and updates the information contained in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus. The second part is the accompanying prospectus, which provides more general information about our common stock and other securities that do not pertain to this offering of common stock. Before buying any of the common stock that we are offering, we urge you to carefully read this prospectus supplement, together with the information incorporated by reference as described under the headings “Where You Can Find More Information” and “Information Incorporated by Reference” in this prospectus supplement. 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 supplement, on the one hand, and the information contained in any document incorporated by reference into this prospectus supplement that was filed with the SEC before the date of this prospectus supplement, on the other hand, you should rely on the information in this prospectus supplement. 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 supplement—the statement in the document having the later date modifies or supersedes the earlier statement.

We have not authorized anyone to provide you with information in addition to or different from that contained in or incorporated by reference in this prospectus supplement, the accompanying prospectus and in any related free writing prospectus that we have authorized for use in connection with this offering and we take no responsibility for any other information others may give you. This prospectus supplement is an offer to sell only the securities offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. You should assume that the information in this prospectus supplement is accurate only as of the date on the front of the document and that any information incorporated by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus supplement or any sale of a security.

This prospectus supplement contains or incorporates by reference summaries of certain provisions contained in some of the documents described herein, but reference is made to the actual documents for complete information. All of the summaries are qualified in their entirety by the actual documents. Copies of some of the documents referred to herein have been filed, will be filed or will be incorporated by reference as exhibits to the registration statement of which this prospectus supplement is a part, and you may obtain copies of those documents as described below under the heading “Where You Can Find More Information”.

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights certain information about us, this offering and selected information contained elsewhere in or incorporated by reference into this prospectus supplement. This summary is not complete and does not contain all of the information that you should consider before deciding whether to invest in our common stock. For a more complete understanding of our company and this offering, we encourage you to read and consider carefully the more detailed information in this prospectus supplement, including the information incorporated by reference in this prospectus supplement, including the information under the heading “Risk Factors” in this prospectus supplement on page S-5 and in the documents incorporated by reference into this prospectus supplement.

Company Overview

We are a multi-asset, clinical-stage biopharmaceutical company focused on identifying, developing and commercializing novel treatments for multi-drug resistant, or MDR, bacterial infections. Our most advanced product candidate, SPR994 (also called tebipenem pivoxil hydrobromide), is designed to be the first broad-spectrum 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 also have a platform technology known as our Potentiator Platform, which includes two intravenous, or IV-administered agents, SPR206 and SPR741, that are active either alone or in combination with other standard of care agents and are designed to treat MDR Gram-negative bacteria in the hospital. In addition, we are developing SPR720, an oral antibiotic designed for the treatment of a rare, orphan disease called pulmonary non-tuberculous mycobacterial infection, or NTM infection. In February 2019, SPR720 was granted Qualified Infectious Disease Product (QIDP) designation by the U.S. Food and Drug Administration for both the treatment of lung infections caused by nontuberculous mycobacteria and *Mycobacterium tuberculosis*. 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.

Corporate Information

We were formed as Spero Therapeutics, LLC in December 2013 under the laws of the State of Delaware. In June 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. 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 ™ 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	<p>Shares of our common stock having an aggregate offering price of up to \$10,000,000, which are being offered in up to two closings as follows:</p> <ul style="list-style-type: none">• In the initial closing of this offering, we are selling 465,983 shares of our common stock at a price of \$10.73 per share to an investor pursuant to the Purchase Agreement.• As further described in this prospectus supplement, in the second closing, we will sell up to an additional \$5,000,000 of our common stock to such investor pursuant to the Purchase Agreement at a price per share equal to the volume weighted average price of our common stock for the ten consecutive trading days immediately preceding the date of the second closing. The date of the second closing will be the earlier of (i) the eleventh trading day immediately following the SPR994 Data Disclosure Date or (ii) June 30, 2020, subject to the satisfaction of certain conditions set forth in the Purchase Agreement. Pursuant to the Purchase Agreement, the investor shall have no obligation to purchase shares of our common stock in the second closing, and the second closing shall not occur, if, prior to and continuing as of the SPR994 Data Disclosure Date, we shall have ceased all research and development (including clinical development) of SPR720.
Common stock to be outstanding immediately following the initial closing of this offering	17,801,049 shares
Common stock to be outstanding immediately following the second closing of this offering	18,288,853 shares, assuming sales of (i) 465,983 shares of our common stock in the initial closing of this offering and (ii) 487,804 shares of our common stock in the second closing of this offering at a price of \$10.25 per share, which was the last reported sale price of our common stock on The Nasdaq Global Select Market on June 11, 2019. The actual number of shares issued will vary depending on the sales price of our common stock in the second closing of this offering and whether we complete the second closing, as further described in this prospectus supplement.
Use of proceeds	We currently intend to use the net proceeds from this offering to advance our SPR720 therapeutic program. See “Use of Proceeds” on page S-10 of this prospectus supplement.
Risk factors	Investing in our common stock involves significant risks. See “Risk Factors” on page S-5 of this prospectus supplement, and under similar headings in other documents incorporated by reference into this prospectus supplement.
The Nasdaq Global Select Market Symbol	“SPRO”

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The number of shares of common stock shown above to be outstanding after this offering is based on 17,335,066 shares of our common stock issued and outstanding as of March 31, 2019, and excludes:

- 2,220,000 shares of common stock issuable upon conversion of outstanding shares of our Series A Convertible Preferred Stock as of March 31, 2019;
- 1,000,000 shares of common stock issuable upon conversion of 1,000 shares of our Series B Convertible Preferred Stock as of March 31, 2019;
- 3,082,943 shares of common stock issuable upon exercise of outstanding options as of March 31, 2019, having a weighted average exercise price of \$7.88 per share, of which 992,362 shares were vested as of such date;
- 50,000 shares of common stock issuable upon the vesting and release of outstanding restricted stock units as of March 31, 2019; and
- 435,488 shares of common stock reserved for future issuance as of March 31, 2019 under our 2017 Stock Incentive Plan, as amended, and our 2019 Inducement Equity Incentive 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 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 supplement and the accompanying prospectus, the information and documents incorporated by reference therein 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 supplement and the accompanying 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

We cannot guarantee that the second closing of this offering will be completed or, if so, at what price.

Whether we complete the second closing of this offering depends on certain conditions being met. There can be no assurance that these conditions will be met. If we complete the second closing, the pricing of the shares issued in the second closing will be based on a volume weighted average price of our common stock around such time, which could be less than the price at which the shares are being issued in the initial closing of this offering. The amount of shares sold in the second closing will depend on the foregoing.

If we fail to raise sufficient capital in this offering, we may need to seek alternative financing when market conditions permit. Such financing may not be available on favorable terms, or at all. The actual amount of funds that we will need and the timing of any such investment will be determined by many factors, some of which are beyond our control.

Our management may have 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.

Although the net proceeds from this offering are intended to be used to advance our SPR720 therapeutic program, there may be circumstances where a reallocation of funds is necessary. In such circumstances, our management will have 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.

You will experience immediate dilution in the book value per share of the common stock purchased in this offering.

The price per share of our common stock being offered in the initial closing may be higher than the net tangible book value per share of our common stock outstanding prior to the initial closing. Based on the offering

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price of \$10.73 per share in the initial closing and our net tangible book value as of March 31, 2019 of \$6.54 per share, if you purchase shares of common stock in the initial closing of this offering, and after deducting estimated offering expenses payable by us, you will suffer immediate and substantial dilution of \$4.09 per share, representing the difference between the as adjusted net tangible book value per share of our common stock as of March 31, 2019 after giving effect to the initial closing of this offering.

The price per share of our common stock being offered in the second closing may be higher than the net tangible book value per share of our common stock outstanding prior to the second closing. Assuming that an aggregate of 487,804 shares are sold in the second closing at a price of \$10.25 per share, the last reported sale price of our common stock on The Nasdaq Global Select Market on June 11, 2019, for aggregate proceeds of approximately \$5,000,000, and after deducting estimated offering expenses payable by us, you will suffer immediate and substantial dilution of \$3.74 per share, representing the difference between the as adjusted net tangible book value per share of our common stock as of March 31, 2019 after giving effect to the second closing of this offering at the assumed offering price. The foregoing calculation is based on net tangible book value as of March 31, 2019, and net tangible book value as of the second closing could be substantially different.

You will experience additional dilution upon the exercise of options, as well as upon the vesting of outstanding restricted stock units, including those options currently outstanding and those granted in the future, and the issuance of restricted stock or other equity awards under our stock incentive plans. See the section entitled "Dilution" for a more detailed discussion of the dilution you will incur if you purchase shares in this offering.

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

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.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be your sole source of gain.

We have never paid or declared any cash dividends on our capital stock. We currently intend to retain earnings, if any, to finance the growth and development of our business and we do not anticipate paying any cash dividends in the foreseeable future. As a result, only appreciation of the price of our common stock will provide a return to our stockholders.

SECOND CLOSING

We are offering up to an aggregate of \$10,000,000 of our common stock in up to two closings.

In the initial closing, we are offering 465,983 shares of our common stock at an offering price of \$10.73 per share directly to an investor pursuant to the Purchase Agreement. The total gross proceeds to us from the initial closing, before expenses, will be approximately \$5,000,000.

In the second closing, we will sell up to an additional \$5,000,000 of our common stock to such investor pursuant to the Purchase Agreement at a price per share equal to the volume weighted average price of our common stock for the ten consecutive trading days immediately preceding the date of the second closing. The date of the second closing will be the earlier of (i) the eleventh trading day immediately following the date of our public announcement of pharmacokinetic data from the lead-in cohort in our pivotal Phase 3 clinical trial of SPR994, or the SPR994 Data Disclosure Date, or (ii) June 30, 2020, subject to the satisfaction of certain conditions set forth in the Purchase Agreement. Pursuant to the Purchase Agreement, the investor shall have no obligation to purchase shares of our common stock in the second closing, and the second closing shall not occur, if, prior to and continuing as of the SPR994 Data Disclosure Date, we shall have ceased all research and development (including clinical development) of SPR720.

In no event shall we be obligated to issue a number of shares of common stock that, when combined with the shares of common stock issued in the initial closing of this offering, would require approval of our stockholders pursuant to Nasdaq Rule 5635. Rather, in such case, we would be obligated to issue the maximum number of shares of common stock, as determined in accordance with the Purchase Agreement and pursuant to its other terms, that could be issued without requiring approval of our stockholders pursuant to Nasdaq Rule 5635.

CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the documents incorporated by reference therein include forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or 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 supplement and incorporated by reference in this prospectus supplement, 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 supplement, 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;
- 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 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;
- whether the second closing will be completed and the number of shares of our common stock that may be sold in this offering; 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

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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 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 estimate that the net proceeds to us from this offering will be an aggregate of \$9.9 million, assuming the completion of both closings and after deducting estimated offering expenses payable by us. We currently intend to use the net proceeds from this offering to advance our SPR720 therapeutic program.

Although as of the date of this prospectus supplement we anticipate that we will use the net proceeds from this offering as described above, there may be circumstances where a reallocation of funds is necessary. Due to the uncertainties inherent in the clinical development process and other factors, it is difficult to estimate with certainty the exact amounts of the net proceeds from this offering that may be used for the above purposes. The amounts and timing of our actual expenditures will depend upon numerous factors, including the status of and results from clinical trials, unforeseen cash needs and the factors described under the heading “Risk Factors” in this prospectus supplement and incorporated by reference from our most recent annual report on Form 10-K. In such circumstances where a reallocation of funds is necessary, our management will have discretion in applying the net proceeds from this offering and investors will be relying on the judgment of our management regarding the application of the net proceeds from this offering.

DILUTION

As of March 31, 2019, our net tangible book value was \$113.3 million, or \$6.54 per share of common stock. Net tangible book value per share represents the amount of our total tangible assets less total liabilities, divided by 17,335,066, the number of shares of common stock outstanding as of March 31, 2019. Dilution with respect to net tangible book value per share represents the difference between the amount per share paid by purchaser of shares of common stock in this offering and the net tangible book value per share of our common stock immediately after this offering.

Initial Closing

After giving effect to the issuance and sale of 465,983 shares of our common stock in the initial closing of this offering at the offering price of \$10.73 per share, and after deducting estimated offering expenses payable by us, our as adjusted net tangible book value as of March 31, 2019 would have been approximately \$118.3 million, or \$6.64 per share. This represents an immediate increase in as adjusted net tangible book value to existing stockholders of \$0.10 per share and an immediate dilution to the new investor purchasing common stock in the initial closing of this offering of \$4.09 per share. The following table illustrates the foregoing on a per share basis:

Offering price per share		\$10.73
Net tangible book value per share as of March 31, 2019	\$6.54	
Increase per share attributable to new investor purchasing shares in the initial closing of this offering	<u>\$0.10</u>	
As adjusted net tangible book value per share after the initial closing of this offering	\$	<u>6.64</u>
Dilution per share to new investor purchasing shares in the initial closing of this offering		\$ 4.09

Initial and Second Closings

After giving effect to the issuance and sale of (i) 465,983 shares of our common stock in the initial closing of this offering at the offering price of \$10.73 per share and (ii) 487,804 shares of our common stock in the second closing of this offering at an assumed offering price of \$10.25 per share, which was the closing price of our common stock as reported on The Nasdaq Global Select Market on June 11, 2019, and after deducting estimated offering expenses payable by us, our as adjusted net tangible book value as of March 31, 2019 would have been approximately \$123.2 million, or \$6.74 per share. This represents an immediate increase in as adjusted net tangible book value to existing stockholders of \$0.20 per share and an immediate dilution to the new investor purchasing common stock in the initial and second closings of this offering of \$3.74 per share. The following table illustrates the foregoing on a per share basis:

Assumed offering price per share		\$10.48
Net tangible book value per share as of March 31, 2019	\$6.54	
Increase per share attributable to new investor purchasing shares in this offering	<u>\$0.20</u>	
As adjusted net tangible book value per share after the second closing of this offering	\$	<u>6.74</u>
Dilution per share to new investor purchasing shares in the initial and second closings of this offering		\$ 3.74

Each \$1.00 increase in the assumed offering price of \$10.25 per share in the second closing, which was the last reported sale price of our common stock on The Nasdaq Global Select Market on June 11, 2019, would increase the as-adjusted net tangible book value per share by approximately \$0.01 per share and would increase the dilution per share to investors by approximately \$0.49 per share. Each \$1.00 decrease in the assumed offering price of \$10.25 per share in the second closing would decrease on the as-adjusted net tangible book value per share by approximately \$0.02 per share and would decrease the dilution per share to investors by approximately \$0.52 per share.

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The above discussion and table are based on 17,335,066 shares of our common stock issued and outstanding as of March 31, 2019, and excludes:

- 2,220,000 shares of common stock issuable upon conversion of outstanding shares of our Series A Convertible Preferred Stock as of March 31, 2019;
- 1,000,000 shares of common stock issuable upon conversion of 1,000 shares of our Series B Convertible Preferred Stock as of March 31, 2019;
- 3,082,943 shares of common stock issuable upon exercise of outstanding options as of March 31, 2019, having a weighted average exercise price of \$7.88 per share, of which 992,362 shares were vested as of such date;
- 50,000 shares of common stock issuable upon the vesting and release of outstanding restricted stock units as of March 31, 2019; and
- 435,488 shares of common stock reserved for future issuance as of March 31, 2019 under our 2017 Stock Incentive Plan, as amended, and our 2019 Inducement Equity Incentive Plan.

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.

PLAN OF DISTRIBUTION

Pursuant to the Purchase Agreement, we are offering up to an aggregate of \$10,000,000 of our common stock, \$0.001 par value per share, in up to two closings. The shares of common stock offered hereby are being sold directly to Novo Holdings A/S and not through a placement agent, underwriter or securities broker or dealer, and we are therefore not paying any underwriting discounts, commissions, concessions or similar compensation for the sale and distribution of the common stock being offered hereby. The total gross proceeds to us from the initial closing, before expenses, will be approximately \$5,000,000. On the dates of each of the initial and second closings of this offering, we will issue the number of shares of common stock to be issued in such closing to Novo Holdings A/S and we will receive funds in the amount of the aggregate purchase price of such shares of common stock being sold in such closing. The estimated offering expenses payable by us for this offering are approximately \$125,000.

We have entered into the Purchase Agreement between us and Novo Holdings A/S covering the sale of the shares offered under this prospectus supplement. A copy of the Purchase Agreement will be included as an exhibit to a Current Report on Form 8-K that will be filed with the SEC in connection with the closing of this offering, which we expect will take place on or about June 14, 2019.

The representations, warranties and covenants contained in the Purchase Agreement were made solely for the benefit of us and Novo Holdings A/S. In addition, such representations, warranties and covenants (i) are intended as a way of allocating the risk between us and Novo Holdings A/S and not as statements of fact, and (ii) may apply standards of materiality in a way that is different from what may be viewed as material by stockholders of, or other investors in, our company. Moreover, information concerning the subject matter of the representations and warranties may change after the date of the Purchase Agreement, which subsequent information may or may not be fully reflected in public disclosures.

The offering of the shares of common stock by us to Novo Holdings A/S under the Purchase Agreement is registered pursuant to our shelf registration statement on Form S-3 (File No. 333-228661), as declared effective by the SEC on December 11, 2018, and as to which this prospectus supplement relates.

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

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

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 supplement.

EXPERTS

The financial statements incorporated in this prospectus supplement by reference to the Annual Report on Form 10-K for the year ended December 31, 2018 have been so incorporated in reliance on the report (which contains an explanatory paragraph relating to the Company's requirement for additional financing to fund future operations 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 web site at <http://www.sec.gov>.

This prospectus supplement is part of a registration statement we filed with the SEC. This prospectus supplement 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 on us and our consolidated subsidiaries and the securities we are offering. Statements in this prospectus supplement 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.

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

INFORMATION INCORPORATED 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 supplement and the accompanying 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 supplement and the accompanying prospectus. This prospectus supplement and the accompanying prospectus omit 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 supplement and accompanying prospectus. Statements in this prospectus supplement and accompanying 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, 2018, filed with the SEC on March 14, 2019;
- the information incorporated by reference into our Annual Report on Form 10-K for the fiscal year ended December 31, 2018 from our [definitive Proxy Statement](#) for our 2019 Annual Meeting of Stockholders, filed with the SEC on April 26, 2019;
- our Quarterly Report on [Form 10-Q](#) for the fiscal quarter ended March 31, 2019, filed with the SEC on May 9, 2019;
- our Current Reports on Form 8-K (and amendments thereto), filed with the SEC on [January 7, 2019](#), [March 19, 2019](#), [March 29, 2019](#), [April 18, 2019](#), [June 6, 2019](#) and [June 13, 2019](#) (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 supplement or the accompanying 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 supplement or the accompanying 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 herein or in a document incorporated or deemed to be incorporated by reference into this document will be deemed to be modified or superseded for purposes of the document to the extent that a statement contained in this document or any other subsequently filed document that is deemed to be incorporated by reference into this document modifies or supersedes the statement.

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

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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.

You should rely only on information contained in, or incorporated by reference into, this prospectus supplement or the accompanying prospectus. We have not authorized anyone to provide you with information different from that contained in or incorporated by reference in this prospectus supplement or the accompanying 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.

PROSPECTUS

Spero Therapeutics, Inc.

\$200,000,000

**COMMON STOCK
PREFERRED STOCK
DEBT SECURITIES
WARRANTS
RIGHTS
UNITS**

This prospectus will allow us to issue, from time to time at prices and on terms to be determined at or prior to the time of the offering, up to \$200,000,000 of any combination of the securities described in this prospectus, either individually or in units. We may also offer common stock or preferred stock upon conversion of or exchange for the debt securities; common stock upon conversion of or exchange for preferred stock; or common stock, preferred stock or debt securities upon the exercise of warrants or rights.

This prospectus describes the general terms of these securities and the general manner in which these securities will be offered. We will provide you with the specific terms of any offering in one or more supplements to this prospectus. The prospectus supplements will also describe the specific manner in which these securities will be offered and may also supplement, update or amend information contained in this document. You should read this prospectus and any prospectus supplement, as well as any documents incorporated by reference into this prospectus or any prospectus supplement, carefully before you invest.

Our securities may be sold directly by us to you, through agents designated from time to time or to or through underwriters or dealers. For additional information on the methods of sale, you should refer to the section entitled "Plan of Distribution" in this prospectus and in the applicable prospectus supplement. If any underwriters or agents are involved in the sale of our securities with respect to which this prospectus is being delivered, the names of such underwriters or agents and any applicable fees, commissions or discounts and over-allotment options will be set forth in a prospectus supplement. The price to the public of such securities and the net proceeds that we expect to receive from such sale will also be set forth in a prospectus supplement.

Our common stock is listed on The Nasdaq Global Select Market under the symbol "SPRO." On November 30, 2018, the last reported sale price of our common stock was \$8.18 per share. The applicable prospectus supplement will contain information, where applicable, as to any other listing, if any, on The Nasdaq Global Select Market or any securities market or other securities exchange of the securities covered by the prospectus supplement. Prospective purchasers of our securities are urged to obtain current information as to the market prices of our securities, where applicable.

Investing in our securities involves a high degree of risk. See "[Risk Factors](#)" included in any accompanying prospectus supplement and in the documents incorporated by reference in this prospectus for a discussion of the factors you should carefully consider before deciding to purchase these securities.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is December 3, 2018.

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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 offer shares of our common stock and preferred stock, various series of debt securities and/or warrants or rights to purchase any such securities, either individually or in units, in one or more offerings, with a total value of up to \$200,000,000. This prospectus provides you with a general description of the securities we may offer. Each time we offer a type or series of securities under this prospectus, we will provide a prospectus supplement that will contain specific information about the terms of that offering.

This prospectus does not contain all of the information included in the registration statement. For a more complete understanding of the offering of the securities, you should refer to the registration statement, including its exhibits. The prospectus supplement may also add, update or change information contained or incorporated by reference in this prospectus. However, no prospectus supplement will offer a security that is not registered and described in this prospectus at the time of its effectiveness. This prospectus, together with the applicable prospectus supplements and the documents incorporated by reference into this prospectus, includes all material information relating to the offering of securities under this prospectus. You should carefully read this prospectus, the applicable prospectus supplement, the information and documents incorporated herein by reference and the additional information under the heading “Where You Can Find More Information” before making an investment decision.

You should rely only on the information we have provided or incorporated by reference in this prospectus or any prospectus supplement. We have not authorized anyone to provide you with information different from that contained or incorporated by reference in this prospectus. No dealer, salesperson or other person is authorized to give any information or to represent anything not contained or incorporated by reference in this prospectus. You must not rely on any unauthorized information or representation. This prospectus is an offer to sell only the securities offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. You should assume that the information in this prospectus or any prospectus supplement is accurate only as of the date on the front of the document and that any information we have incorporated herein by reference is accurate only as of the date of the document incorporated by reference, regardless of the time of delivery of this prospectus or any sale of a security.

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.

This prospectus may not be used to consummate sales of our securities, unless it is accompanied by a prospectus supplement. To the extent there are inconsistencies between any prospectus supplement, this prospectus and any documents incorporated by reference, the document with the most recent date will control.

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 or included in any applicable prospectus supplement. Investing in our securities involves risks. Therefore, carefully consider the risk factors set forth in any prospectus supplements and in our most recent annual and quarterly filings with the SEC, as well as other information in this prospectus and any prospectus supplements 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 novel treatments for multi-drug resistant, or MDR, bacterial infections. Our most advanced product candidate, SPR994, is designed to be the first broad-spectrum 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 also have a platform technology known as our Potentiator Platform that we believe will enable us to develop drugs that will expand the spectrum and potency of existing antibiotics, including formerly inactive antibiotics, against Gram-negative bacteria. Our lead product candidates generated from our Potentiator Platform are two intravenous, or IV-, administered agents, SPR741 and SPR206, designed to treat MDR Gram-negative infections in the hospital setting. In addition, we are developing SPR720, an oral antibiotic designed for the treatment of a disease called pulmonary non-tuberculous mycobacterial infections, or NTM. 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 31 of this prospectus.

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. 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 ™ 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.

Offerings Under This Prospectus

Under this prospectus, we may offer shares of our common stock and preferred stock, various series of debt securities and/or warrants or rights to purchase any of such securities, either individually or in units, with a total value of up to \$200,000,000, from time to time at prices and on terms to be determined by market conditions at the time of the offering. This prospectus provides you with a general description of the securities we may offer. Each time we offer a type or series of securities under this prospectus, we will provide a prospectus supplement that will describe the specific amounts, prices and other important terms of the securities, including, to the extent applicable:

- designation or classification;
- aggregate principal amount or aggregate offering price;
- maturity, if applicable;
- rates and times of payment of interest or dividends, if any;
- redemption, conversion or sinking fund terms, if any;
- voting or other rights, if any; and
- conversion or exercise prices, if any.

The prospectus supplement also may add, update or change information contained in this prospectus or in documents we have incorporated by reference into this prospectus. However, no prospectus supplement will fundamentally change the terms that are set forth in this prospectus or offer a security that is not registered and described in this prospectus at the time of its effectiveness.

We may sell the securities directly to investors or to or through agents, underwriters or dealers. We, and our agents or underwriters, reserve the right to accept or reject all or part of any proposed purchase of securities. If we offer securities through agents or underwriters, we will include in the applicable prospectus supplement:

- the names of those agents or underwriters;
- applicable fees, discounts and commissions to be paid to them;
- details regarding over-allotment options, if any; and
- the net proceeds to us.

This prospectus may not be used to consummate a sale of any securities unless it is accompanied by a prospectus supplement.

RISK FACTORS

Investing in our securities involves significant risk. The prospectus supplement applicable to each offering of our securities will contain a discussion of the risks applicable to an investment in Spero. Prior to making a decision about investing in our securities, you should carefully consider the specific factors discussed under the heading “Risk Factors” in the applicable prospectus supplement, together with all of the other information contained or incorporated by reference in the prospectus supplement or appearing or incorporated by reference in this prospectus. You should also consider the risks, uncertainties and assumptions discussed under the heading “Risk Factors” included 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 that we have filed with the SEC, all of which are incorporated herein by reference, and which may be amended, supplemented or superseded from time to time by other reports we file with the SEC in the future. The risks and uncertainties we have described are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our operations. The occurrence of any of these risks might cause you to lose all or part of your investment in the offered securities.

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 of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or 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;
- 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 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

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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 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

Unless otherwise indicated in the applicable prospectus supplement, we intend to use any net proceeds from the sale of securities 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. We have not determined the amounts we plan to spend on any of the areas listed above or the timing of these expenditures. 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. Pending application of the net proceeds as described above, we may initially invest the net proceeds in short-term, investment-grade, interest-bearing securities or apply them to the reduction of short-term indebtedness.

PLAN OF DISTRIBUTION

We may offer securities under this prospectus from time to time pursuant to underwritten public offerings, negotiated transactions, block trades or a combination of these methods. We may sell the securities (1) through underwriters or dealers, (2) through agents or (3) directly to one or more purchasers, or through a combination of such methods. We may distribute the securities from time to time in one or more transactions at:

- a fixed price or prices, which may be changed from time to time;
- market prices prevailing at the time of sale;
- prices related to the prevailing market prices; or
- negotiated prices.

We may directly solicit offers to purchase the securities being offered by this prospectus. We may also designate agents to solicit offers to purchase the securities from time to time, and may enter into arrangements for “at-the-market,” equity line or similar transactions. We will name in a prospectus supplement any underwriter or agent involved in the offer or sale of the securities.

If we utilize a dealer in the sale of the securities being offered by this prospectus, we will sell the securities to the dealer, as principal. The dealer may then resell the securities to the public at varying prices to be determined by the dealer at the time of resale.

If we utilize an underwriter in the sale of the securities being offered by this prospectus, we will execute an underwriting agreement with the underwriter at the time of sale, and we will provide the name of any underwriter in the prospectus supplement which the underwriter will use to make resales of the securities to the public. In connection with the sale of the securities, we, or the purchasers of the securities for whom the underwriter may act as agent, may compensate the underwriter in the form of underwriting discounts or commissions. The underwriter may sell the securities to or through dealers, and the underwriter may compensate those dealers in the form of discounts, concessions or commissions.

With respect to underwritten public offerings, negotiated transactions and block trades, we will provide in the applicable prospectus supplement information regarding any compensation we pay to underwriters, dealers or agents in connection with the offering of the securities, and any discounts, concessions or commissions allowed by underwriters to participating dealers. Underwriters, dealers and agents participating in the distribution of the securities may be deemed to be underwriters within the meaning of the Securities Act, and any discounts and commissions received by them and any profit realized by them on resale of the securities may be deemed to be underwriting discounts and commissions. We may enter into agreements to indemnify underwriters, dealers and agents against civil liabilities, including liabilities under the Securities Act, or to contribute to payments they may be required to make in respect thereof.

If so indicated in the applicable prospectus supplement, we will authorize underwriters, dealers or other persons acting as our agents to solicit offers by certain institutions to purchase securities from us pursuant to delayed delivery contracts providing for payment and delivery on the date stated in each applicable prospectus supplement. Each contract will be for an amount not less than, and the aggregate amount of securities sold pursuant to such contracts shall not be less nor more than, the respective amounts stated in each applicable prospectus supplement. Institutions with whom the contracts, when authorized, may be made include commercial and savings banks, insurance companies, pension funds, investment companies, educational and charitable institutions and other institutions, but shall in all cases be subject to our approval. Delayed delivery contracts will not be subject to any conditions except that:

- the purchase by an institution of the securities covered under that contract shall not at the time of delivery be prohibited under the laws of the jurisdiction to which that institution is subject; and

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- if the securities are also being sold to underwriters acting as principals for their own account, the underwriters shall have purchased such securities not sold for delayed delivery. The underwriters and other persons acting as our agents will not have any responsibility in respect of the validity or performance of delayed delivery contracts.

One or more firms, referred to as “remarketing firms,” may also offer or sell the securities, if a prospectus supplement so indicates, in connection with a remarketing arrangement upon their purchase. Remarketing firms will act as principals for their own accounts or as our agents. These remarketing firms will offer or sell the securities in accordance with the terms of the securities. Each prospectus supplement will identify and describe any remarketing firm and the terms of its agreement, if any, with us and will describe the remarketing firm’s compensation. Remarketing firms may be deemed to be underwriters in connection with the securities they remarket. Remarketing firms may be entitled under agreements that may be entered into with us to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, and may be customers of, engage in transactions with or perform services for us in the ordinary course of business.

Certain underwriters may use this prospectus and any accompanying prospectus supplement for offers and sales related to market-making transactions in the securities. These underwriters may act as principal or agent in these transactions, and the sales will be made at prices related to prevailing market prices at the time of sale. Any underwriters involved in the sale of the securities may qualify as “underwriters” within the meaning of Section 2(a)(11) of the Securities Act. In addition, the underwriters’ commissions, discounts or concessions may qualify as underwriters’ compensation under the Securities Act and the rules of the Financial Industry Regulatory Authority, Inc., or FINRA.

Shares of our common stock sold pursuant to the registration statement of which this prospectus is a part will be authorized for listing and trading on The Nasdaq Global Select Market. The applicable prospectus supplement will contain information, where applicable, as to any other listing, if any, on The Nasdaq Global Select Market or any securities market or other securities exchange of the securities covered by the prospectus supplement. Underwriters may make a market in our common stock, but will not be obligated to do so and may discontinue any market making at any time without notice. We can make no assurance as to the liquidity of or the existence, development or maintenance of trading markets for any of the securities.

In order to facilitate the offering of the securities, certain persons participating in the offering may engage in transactions that stabilize, maintain or otherwise affect the price of the securities. This may include over-allotments or short sales of the securities, which involve the sale by persons participating in the offering of more securities than we sold to them. In these circumstances, these persons would cover such over-allotments or short positions by making purchases in the open market or by exercising their over-allotment option. In addition, these persons may stabilize or maintain the price of the securities by bidding for or purchasing the applicable security in the open market or by imposing penalty bids, whereby selling concessions allowed to dealers participating in the offering may be reclaimed if the securities sold by them are repurchased in connection with stabilization transactions. The effect of these transactions may be to stabilize or maintain the market price of the securities at a level above that which might otherwise prevail in the open market. These transactions may be discontinued at any time.

The underwriters, dealers and agents may engage in other transactions with us, or perform other services for us, in the ordinary course of their business.

DESCRIPTION OF COMMON STOCK

We are authorized to issue 60,000,000 shares of common stock, par value \$0.001 per share. As of November 30, 2018, we had 17,205,962 shares of common stock outstanding and approximately 14 stockholders of record of our common stock.

The following summary of certain provisions of our common 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.

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.”

DESCRIPTION OF PREFERRED STOCK

The following description of our preferred stock and the description of the terms of any particular series of preferred stock that we choose to issue hereunder are not complete. These descriptions are qualified in their entirety by reference to our amended and restated certificate of incorporation and the certificate of designation relating to any series of preferred stock issued by us. The rights, preferences, privileges and restrictions of the preferred stock of each series will be fixed by the certificate of designation relating to that series.

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.

Our board of directors may specify the following characteristics of any preferred stock:

- the maximum number of shares;
- the designation of the shares;
- the annual dividend rate, if any, whether the dividend rate is fixed or variable, the date or dates on which dividends will accrue, the dividend payment dates, and whether dividends will be cumulative;
- the price and the terms and conditions for redemption, if any, including redemption at the option of Spero or at the option of the holders, including the time period for redemption, and any accumulated dividends or premiums;
- the liquidation preference, if any, and any accumulated dividends upon the liquidation, dissolution or winding up of Spero’s affairs;
- any sinking fund or similar provision, and, if so, the terms and provisions relating to the purpose and operation of the fund;
- the terms and conditions, if any, for conversion or exchange of shares of any other class or classes of Spero’s capital stock or any series of any other class or classes, or of any other series of the same class, or any other securities or assets, including the price or the rate of conversion or exchange and the method, if any, of adjustment;
- the voting rights;
- any or all other preferences and relative, participating, optional or other special rights, privileges or qualifications, limitations or restrictions; and
- any preferred stock issued will be fully paid and nonassessable upon issuance.

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.

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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 any of our 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 *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 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.

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.

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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

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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, 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.

Transfer Agent and Registrar

The transfer agent and registrar for our Series A Preferred Stock and Series B Preferred Stock is Computershare Trust Company, N.A. The transfer agent and registrar for any additional series of preferred stock will be set forth in the applicable prospectus supplement.

DESCRIPTION OF DEBT SECURITIES

The following description, together with the additional information we include in any applicable prospectus supplements, summarizes the material terms and provisions of the debt securities that we may offer under this prospectus. While the terms we have summarized below will apply generally to any future debt securities we may offer pursuant to this prospectus, we will describe the particular terms of any debt securities that we may offer in more detail in the applicable prospectus supplement. If we so indicate in a prospectus supplement, the terms of any debt securities offered under such prospectus supplement may differ from the terms we describe below, and to the extent the terms set forth in a prospectus supplement differ from the terms described below, the terms set forth in the prospectus supplement shall control.

We may sell from time to time, in one or more offerings under this prospectus, debt securities, which may be senior or subordinated. We will issue any such senior debt securities under a senior indenture that we will enter into with a trustee to be named in the senior indenture. We will issue any such subordinated debt securities under a subordinated indenture, which we will enter into with a trustee to be named in the subordinated indenture. We have filed forms of these documents as exhibits to the registration statement, of which this prospectus is a part. We use the term “indentures” to refer to either the senior indenture or the subordinated indenture, as applicable. The indentures will be qualified under the Trust Indenture Act of 1939, as in effect on the date of the indenture. We use the term “debenture trustee” to refer to either the trustee under the senior indenture or the trustee under the subordinated indenture, as applicable.

The following summaries of material provisions of the senior debt securities, the subordinated debt securities and the indentures are subject to, and qualified in their entirety by reference to, all the provisions of the indenture applicable to a particular series of debt securities.

General

Each indenture provides that debt securities may be issued from time to time in one or more series and may be denominated and payable in foreign currencies or units based on or relating to foreign currencies. Neither indenture limits the amount of debt securities that may be issued thereunder, and each indenture provides that the specific terms of any series of debt securities shall be set forth in, or determined pursuant to, an authorizing resolution and/or a supplemental indenture, if any, relating to such series.

We will describe in each prospectus supplement the following terms relating to a series of debt securities:

- the title or designation;
- the aggregate principal amount and any limit on the amount that may be issued;
- the currency or units based on or relating to currencies in which debt securities of such series are denominated and the currency or units in which principal or interest or both will or may be payable;
- whether we will issue the series of debt securities in global form, the terms of any global securities and who the depositary will be;
- the maturity date and the date or dates on which principal will be payable;
- the interest rate, which may be fixed or variable, or the method for determining the rate and the date interest will begin to accrue, the date or dates interest will be payable and the record dates for interest payment dates or the method for determining such dates;
- whether or not the debt securities will be secured or unsecured, and the terms of any secured debt;
- the terms of the subordination of any series of subordinated debt;
- the place or places where payments will be payable;

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- our right, if any, to defer payment of interest and the maximum length of any such deferral period;
- the date, if any, after which, and the price at which, we may, at our option, redeem the series of debt securities pursuant to any optional redemption provisions;
- the date, if any, on which, and the price at which we are obligated, pursuant to any mandatory sinking fund provisions or otherwise, to redeem, or at the holder's option to purchase, the series of debt securities;
- whether the indenture will restrict our ability to pay dividends, or will require us to maintain any asset ratios or reserves;
- whether we will be restricted from incurring any additional indebtedness;
- a discussion of any material or special U.S. federal income tax considerations applicable to a series of debt securities;
- the denominations in which we will issue the series of debt securities, if other than denominations of \$1,000 and any integral multiple thereof; and
- any other specific terms, preferences, rights or limitations of, or restrictions on, the debt securities.

We may issue debt securities that provide for an amount less than their stated principal amount to be due and payable upon declaration of acceleration of their maturity pursuant to the terms of the indenture. We will provide you with information on the federal income tax considerations and other special considerations applicable to any of these debt securities in the applicable prospectus supplement.

Conversion or Exchange Rights

We will set forth in the prospectus supplement the terms, if any, on which a series of debt securities may be convertible into or exchangeable for our common stock or our other securities. We will include provisions as to whether conversion or exchange is mandatory, at the option of the holder or at our option. We may include provisions pursuant to which the number of shares of our common stock or our other securities that the holders of the series of debt securities receive would be subject to adjustment.

Consolidation, Merger or Sale; No Protection in Event of a Change of Control or Highly Leveraged Transaction

The indentures do not contain any covenant that restricts our ability to merge or consolidate, or sell, convey, transfer or otherwise dispose of all or substantially all of our assets. However, any successor to or acquirer of such assets must assume all of our obligations under the indentures or the debt securities, as appropriate.

Unless we state otherwise in the applicable prospectus supplement, the debt securities will not contain any provisions that may afford holders of the debt securities protection in the event we have a change of control or in the event of a highly leveraged transaction (whether or not such transaction results in a change of control), which could adversely affect holders of debt securities.

Events of Default Under the Indenture

The following are events of default under the indentures with respect to any series of debt securities that we may issue:

- if we fail to pay interest when due and our failure continues for 90 days and the time for payment has not been extended or deferred;
- if we fail to pay the principal, or premium, if any, when due and the time for payment has not been extended or delayed;

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- if we fail to observe or perform any other covenant set forth in the debt securities of such series or the applicable indentures, other than a covenant specifically relating to and for the benefit of holders of another series of debt securities, and our failure continues for 90 days after we receive written notice from the debenture trustee or holders of not less than a majority in aggregate principal amount of the outstanding debt securities of the applicable series; and
- if specified events of bankruptcy, insolvency or reorganization occur as to us.

No event of default with respect to a particular series of debt securities (except as to certain events of bankruptcy, insolvency or reorganization) necessarily constitutes an event of default with respect to any other series of debt securities. The occurrence of an event of default may constitute an event of default under any bank credit agreements we may have in existence from time to time. In addition, the occurrence of certain events of default or an acceleration under the indenture may constitute an event of default under certain of our other indebtedness outstanding from time to time.

If an event of default with respect to debt securities of any series at the time outstanding occurs and is continuing, then the trustee or the holders of not less than a majority in principal amount of the outstanding debt securities of that series may, by a notice in writing to us (and to the debenture trustee if given by the holders), declare to be due and payable immediately the principal (or, if the debt securities of that series are discount securities, that portion of the principal amount as may be specified in the terms of that series) of and premium and accrued and unpaid interest, if any, on all debt securities of that series. Before a judgment or decree for payment of the money due has been obtained with respect to debt securities of any series, the holders of a majority in principal amount of the outstanding debt securities of that series (or, at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount of the debt securities of such series represented at such meeting) may rescind and annul the acceleration if all events of default, other than the non-payment of accelerated principal, premium, if any, and interest, if any, with respect to debt securities of that series, have been cured or waived as provided in the applicable indenture (including payments or deposits in respect of principal, premium or interest that had become due other than as a result of such acceleration). We refer you to the prospectus supplement relating to any series of debt securities that are discount securities for the particular provisions relating to acceleration of a portion of the principal amount of such discount securities upon the occurrence of an event of default.

Subject to the terms of the indentures, if an event of default under an indenture shall occur and be continuing, the debenture trustee will be under no obligation to exercise any of its rights or powers under such indenture at the request or direction of any of the holders of the applicable series of debt securities, unless such holders have offered the debenture trustee reasonable indemnity. The holders of a majority in principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the debenture trustee, or exercising any trust or power conferred on the debenture trustee, with respect to the debt securities of that series, provided that:

- the direction so given by the holder is not in conflict with any law or the applicable indenture; and
- subject to its duties under the Trust Indenture Act, the debenture trustee need not take any action that might involve it in personal liability or might be unduly prejudicial to the holders not involved in the proceeding.

A holder of the debt securities of any series will only have the right to institute a proceeding under the indentures or to appoint a receiver or trustee, or to seek other remedies if:

- the holder previously has given written notice to the debenture trustee of a continuing event of default with respect to that series;
- the holders of at least a majority in aggregate principal amount of the outstanding debt securities of that series have made written request, and such holders have offered reasonable indemnity to the debenture trustee to institute the proceeding as trustee; and

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- the debenture trustee does not institute the proceeding, and does not receive from the holders of a majority in aggregate principal amount of the outstanding debt securities of that series (or at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount of the debt securities of such series represented at such meeting) other conflicting directions within 60 days after the notice, request and offer.

These limitations do not apply to a suit instituted by a holder of debt securities if we default in the payment of the principal, premium, if any, or interest on, the debt securities.

We will periodically file statements with the applicable debenture trustee regarding our compliance with specified covenants in the applicable indenture.

Modification of Indenture; Waiver

The debenture trustee and we may change the applicable indenture without the consent of any holders with respect to specific matters, including:

- to fix any ambiguity, defect or inconsistency in the indenture; and
- to change anything that does not materially adversely affect the interests of any holder of debt securities of any series issued pursuant to such indenture.

In addition, under the indentures, the rights of holders of a series of debt securities may be changed by us and the debenture trustee with the written consent of the holders of at least a majority in aggregate principal amount of the outstanding debt securities of each series (or, at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount of the debt securities of such series represented at such meeting) that is affected. However, the debenture trustee and we may make the following changes only with the consent of each holder of any outstanding debt securities affected:

- extending the fixed maturity of the series of debt securities;
- reducing the principal amount, reducing the rate of or extending the time of payment of interest, or any premium payable upon the redemption of any debt securities;
- reducing the principal amount of discount securities payable upon acceleration of maturity;
- making the principal of or premium or interest on any debt security payable in currency other than that stated in the debt security; or
- reducing the percentage of debt securities, the holders of which are required to consent to any amendment or waiver.

Except for certain specified provisions, the holders of at least a majority in principal amount of the outstanding debt securities of any series (or, at a meeting of holders of such series at which a quorum is present, the holders of a majority in principal amount of the debt securities of such series represented at such meeting) may on behalf of the holders of all debt securities of that series waive our compliance with provisions of the indenture. The holders of a majority in principal amount of the outstanding debt securities of any series may on behalf of the holders of all the debt securities of such series waive any past default under the indenture with respect to that series and its consequences, except a default in the payment of the principal of, premium or any interest on any debt security of that series or in respect of a covenant or provision, which cannot be modified or amended without the consent of the holder of each outstanding debt security of the series affected; *provided, however*, that the holders of a majority in principal amount of the outstanding debt securities of any series may rescind an acceleration and its consequences, including any related payment default that resulted from the acceleration.

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Discharge

Each indenture provides that we can elect to be discharged from our obligations with respect to one or more series of debt securities, except for obligations to:

- the transfer or exchange of debt securities of the series;
- replace stolen, lost or mutilated debt securities of the series;
- maintain paying agencies;
- hold monies for payment in trust;
- compensate and indemnify the trustee; and
- appoint any successor trustee.

In order to exercise our rights to be discharged with respect to a series, we must deposit with the trustee money or government obligations sufficient to pay all the principal of, the premium, if any, and interest on, the debt securities of the series on the dates payments are due.

Form, Exchange and Transfer

We will issue the debt securities of each series only in fully registered form without coupons and, unless we otherwise specify in the applicable prospectus supplement, in denominations of \$1,000 and any integral multiple thereof. The indentures provide that we may issue debt securities of a series in temporary or permanent global form and as book-entry securities that will be deposited with, or on behalf of, The Depository Trust Company or another depositary named by us and identified in a prospectus supplement with respect to that series.

At the option of the holder, subject to the terms of the indentures and the limitations applicable to global securities described in the applicable prospectus supplement, the holder of the debt securities of any series can exchange the debt securities for other debt securities of the same series, in any authorized denomination and of like tenor and aggregate principal amount.

Subject to the terms of the indentures and the limitations applicable to global securities set forth in the applicable prospectus supplement, holders of the debt securities may present the debt securities for exchange or for registration of transfer, duly endorsed or with the form of transfer endorsed thereon duly executed if so required by us or the security registrar, at the office of the security registrar or at the office of any transfer agent designated by us for this purpose. Unless otherwise provided in the debt securities that the holder presents for transfer or exchange or in the applicable indenture, we will make no service charge for any registration of transfer or exchange, but we may require payment of any taxes or other governmental charges.

We will name in the applicable prospectus supplement the security registrar, and any transfer agent in addition to the security registrar, that we initially designate for any debt securities. We may at any time designate additional transfer agents or rescind the designation of any transfer agent or approve a change in the office through which any transfer agent acts, except that we will be required to maintain a transfer agent in each place of payment for the debt securities of each series.

If we elect to redeem the debt securities of any series, we will not be required to:

- issue, register the transfer of, or exchange any debt securities of that series during a period beginning at the opening of business 15 days before the day of mailing of a notice of redemption of any debt securities that may be selected for redemption and ending at the close of business on the day of the mailing; or
- register the transfer of or exchange any debt securities so selected for redemption, in whole or in part, except the unredeemed portion of any debt securities we are redeeming in part.

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Information Concerning the Debenture Trustee

The debenture trustee, other than during the occurrence and continuance of an event of default under the applicable indenture, undertakes to perform only those duties as are specifically set forth in the applicable indenture. Upon an event of default under an indenture, the debenture trustee under such indenture must use the same degree of care as a prudent person would exercise or use in the conduct of his or her own affairs. Subject to this provision, the debenture trustee is under no obligation to exercise any of the powers given it by the indentures at the request of any holder of debt securities unless it is offered reasonable security and indemnity against the costs, expenses and liabilities that it might incur.

Payment and Paying Agents

Unless we otherwise indicate in the applicable prospectus supplement, we will make payment of the interest on any debt securities on any interest payment date to the person in whose name the debt securities, or one or more predecessor securities, are registered at the close of business on the regular record date for the interest.

We will pay principal of and any premium and interest on the debt securities of a particular series at the office of the paying agents designated by us, except that unless we otherwise indicate in the applicable prospectus supplement, we will make interest payments by check which we will mail to the holder. Unless we otherwise indicate in a prospectus supplement, we will designate the corporate trust office of the debenture trustee in the City of New York as our sole paying agent for payments with respect to debt securities of each series. We will name in the applicable prospectus supplement any other paying agents that we initially designate for the debt securities of a particular series. We will maintain a paying agent in each place of payment for the debt securities of a particular series.

All money we pay to a paying agent or the debenture trustee for the payment of the principal of or any premium or interest on any debt securities which remains unclaimed at the end of two years after such principal, premium or interest has become due and payable will be repaid to us, and the holder of the security thereafter may look only to us for payment thereof.

Governing Law

The indentures and the debt securities will be governed by and construed in accordance with the laws of the State of New York, except to the extent that the Trust Indenture Act is applicable.

Subordination of Subordinated Debt Securities

Our obligations pursuant to any subordinated debt securities will be unsecured and will be subordinate and junior in priority of payment to certain of our other indebtedness to the extent described in a prospectus supplement. The subordinated indenture does not limit the amount of senior indebtedness we may incur. It also does not limit us from issuing any other secured or unsecured debt.

DESCRIPTION OF WARRANTS

General

We may issue warrants to purchase shares of our common stock, preferred stock and/or debt securities in one or more series together with other securities or separately, as described in the applicable prospectus supplement. Below is a description of certain general terms and provisions of the warrants that we may offer. Particular terms of the warrants will be described in the warrant agreements and the prospectus supplement relating to the warrants.

The applicable prospectus supplement will contain, where applicable, the following terms of and other information relating to the warrants:

- the specific designation and aggregate number of, and the price at which we will issue, the warrants;
- the currency or currency units in which the offering price, if any, and the exercise price are payable;
- the designation, amount and terms of the securities purchasable upon exercise of the warrants;
- if applicable, the exercise price for shares of our common stock and the number of shares of common stock to be received upon exercise of the warrants;
- if applicable, the exercise price for shares of our preferred stock, the number of shares of preferred stock to be received upon exercise, and a description of that series of our preferred stock;
- if applicable, the exercise price for our debt securities, the amount of debt securities to be received upon exercise, and a description of that series of debt securities;
- the date on which the right to exercise the warrants will begin and the date on which that right will expire or, if you may not continuously exercise the warrants throughout that period, the specific date or dates on which you may exercise the warrants;
- whether the warrants will be issued in fully registered form or bearer form, in definitive or global form or in any combination of these forms, although, in any case, the form of a warrant included in a unit will correspond to the form of the unit and of any security included in that unit;
- any applicable material U.S. federal income tax consequences;
- the identity of the warrant agent for the warrants and of any other depositaries, execution or paying agents, transfer agents, registrars or other agents;
- the proposed listing, if any, of the warrants or any securities purchasable upon exercise of the warrants on any securities exchange;
- if applicable, the date from and after which the warrants and the common stock, preferred stock and/or debt securities will be separately transferable;
- if applicable, the minimum or maximum amount of the warrants that may be exercised at any one time;
- information with respect to book-entry procedures, if any;
- the anti-dilution provisions of the warrants, if any;
- any redemption or call provisions;
- whether the warrants may be sold separately or with other securities as parts of units; and
- any additional terms of the warrants, including terms, procedures and limitations relating to the exchange and exercise of the warrants.

Transfer Agent and Registrar

The transfer agent and registrar for any warrants will be set forth in the applicable prospectus supplement.

DESCRIPTION OF RIGHTS

General

We may issue rights to our stockholders to purchase shares of our common stock, preferred stock or the other securities described in this prospectus. We may offer rights separately or together with one or more additional rights, debt securities, preferred stock, common stock or warrants, or any combination of those securities in the form of units, as described in the applicable prospectus supplement. Each series of rights will be issued under a separate rights agreement to be entered into between us and a bank or trust company, as rights agent. The rights agent will act solely as our agent in connection with the certificates relating to the rights of the series of certificates and will not assume any obligation or relationship of agency or trust for or with any holders of rights certificates or beneficial owners of rights. The following description sets forth certain general terms and provisions of the rights to which any prospectus supplement may relate. The particular terms of the rights to which any prospectus supplement may relate and the extent, if any, to which the general provisions may apply to the rights so offered will be described in the applicable prospectus supplement. To the extent that any particular terms of the rights, rights agreement or rights certificates described in a prospectus supplement differ from any of the terms described below, then the terms described below will be deemed to have been superseded by that prospectus supplement. We encourage you to read the applicable rights agreement and rights certificate for additional information before you decide whether to purchase any of our rights. We will provide in a prospectus supplement the following terms of the rights being issued:

- the date of determining the stockholders entitled to the rights distribution;
- the aggregate number of shares of common stock, preferred stock or other securities purchasable upon exercise of the rights;
- the exercise price;
- the aggregate number of rights issued;
- whether the rights are transferrable and the date, if any, on and after which the rights may be separately transferred;
- the date on which the right to exercise the rights will commence, and the date on which the right to exercise the rights will expire;
- the method by which holders of rights will be entitled to exercise;
- the conditions to the completion of the offering, if any;
- the withdrawal, termination and cancellation rights, if any;
- whether there are any backstop or standby purchaser or purchasers and the terms of their commitment, if any;
- whether stockholders are entitled to oversubscription rights, if any;
- any applicable material U.S. federal income tax considerations; and
- any other terms of the rights, including terms, procedures and limitations relating to the distribution, exchange and exercise of the rights, as applicable.

Each right will entitle the holder of rights to purchase for cash the principal amount of shares of common stock, preferred stock or other securities at the exercise price provided in the applicable prospectus supplement. Rights may be exercised at any time up to the close of business on the expiration date for the rights provided in the applicable prospectus supplement.

Holders may exercise rights as described in the applicable prospectus supplement. Upon receipt of payment and the rights certificate properly completed and duly executed at the corporate trust office of the rights agent or

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any other office indicated in the prospectus supplement, we will, as soon as practicable, forward the shares of common stock, preferred stock or other securities, as applicable, purchasable upon exercise of the rights. If less than all of the rights issued in any rights offering are exercised, we may offer any unsubscribed securities directly to persons other than stockholders, to or through agents, underwriters or dealers or through a combination of such methods, including pursuant to standby arrangements, as described in the applicable prospectus supplement.

Rights Agent

The rights agent for any rights we offer will be set forth in the applicable prospectus supplement.

DESCRIPTION OF UNITS

The following description, together with the additional information that we include in any applicable prospectus supplements summarizes the material terms and provisions of the units that we may offer under this prospectus. While the terms we have summarized below will apply generally to any units that we may offer under this prospectus, we will describe the particular terms of any series of units in more detail in the applicable prospectus supplement. The terms of any units offered under a prospectus supplement may differ from the terms described below.

We will incorporate by reference from reports that we file with the SEC, the form of unit agreement that describes the terms of the series of units we are offering, and any supplemental agreements, before the issuance of the related series of units. The following summaries of material terms and provisions of the units are subject to, and qualified in their entirety by reference to, all the provisions of the unit agreement and any supplemental agreements applicable to a particular series of units. We urge you to read the applicable prospectus supplements related to the particular series of units that we may offer under this prospectus, as well as any related free writing prospectuses and the complete unit agreement and any supplemental agreements that contain the terms of the units.

General

We may issue units consisting of common stock, preferred stock, one or more debt securities, warrants or rights for the purchase of common stock, preferred stock and/or debt securities in one or more series, in any combination. Each unit will be issued so that the holder of the unit is also the holder of each security included in the unit. Thus, the holder of a unit will have the rights and obligations of a holder of each security included in the unit. The unit agreement under which a unit is issued may provide that the securities included in the unit may not be held or transferred separately, at any time or at any time before a specified date.

We will describe in the applicable prospectus supplement the terms of the series of units being offered, including:

- the designation and terms of the units and of the securities comprising the units, including whether and under what circumstances those securities may be held or transferred separately;
- any provisions of the governing unit agreement that differ from those described below; and
- any provisions for the issuance, payment, settlement, transfer or exchange of the units or of the securities comprising the units.

The provisions described in this section, as well as those set forth in any prospectus supplement or as described under “Description of Common Stock,” “Description of Preferred Stock,” “Description of Debt Securities,” “Description of Warrants,” and “Description of Rights” will apply to each unit, as applicable, and to any common stock, preferred stock, debt security, warrant or right included in each unit, as applicable.

Unit Agent

The name and address of the unit agent, if any, for any units we offer will be set forth in the applicable prospectus supplement.

Issuance in Series

We may issue units in such amounts and in such numerous distinct series as we determine.

Enforceability of Rights by Holders of Units

Each unit agent will act solely as our agent under the applicable unit agreement and will not assume any obligation or relationship of agency or trust with any holder of any unit. A single bank or trust company may act

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as unit agent for more than one series of units. A unit agent will have no duty or responsibility in case of any default by us under the applicable unit agreement or unit, including any duty or responsibility to initiate any proceedings at law or otherwise, or to make any demand upon us. Any holder of a unit may, without the consent of the related unit agent or the holder of any other unit, enforce by appropriate legal action its rights as holder under any security included in the unit.

**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

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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.

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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.

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.

EXPERTS

The financial statements incorporated in this prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2017 have been so incorporated in reliance on the report (which contains an explanatory paragraph relating to the Company's requirement for additional financing to fund future operations 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 accounting and auditing.

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 web site 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, 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. The documents we are incorporating by reference are:

- our Annual Report on [Form 10-K](#) for the fiscal year ended December 31, 2017, filed with the SEC on April 2, 2018;
- the information incorporated by reference into our Annual Report on [Form 10-K](#) for the year ended December 31, 2017 from our definitive Proxy Statement for our 2018 Annual Meeting of Stockholders, filed with the SEC on April 27, 2018;
- our Quarterly Reports on Form 10-Q for the fiscal quarters ended [March 31, 2018](#), [June 30, 2018](#) and [September 30, 2018](#), filed with the SEC on May 10, 2018, August 9, 2018 and November 8, 2018, respectively;
- our Current Reports on Form 8-K, filed with the SEC on [January 23, 2018](#), [February 1, 2018](#), [June 8, 2018](#), [July 9, 2018](#), [July 16, 2018](#), [July 17, 2018](#), [August 14, 2018](#), [November 13, 2018](#) and [November 16, 2018](#) (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.

In addition, all reports and other documents filed by us pursuant to the Exchange Act after the date of the initial registration statement and prior to effectiveness of the registration statement shall be deemed to be incorporated by reference into this prospectus.

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.

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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.

You should rely only on information contained in, or incorporated by reference into, this prospectus and any prospectus supplement. 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.

Up to \$10,000,000



Common Stock

PROSPECTUS SUPPLEMENT

June 12, 2019
