



4,785,000 Shares of Common Stock

3,215,000 Shares of Series D Convertible Preferred Stock

We are offering 4,785,000 shares of our common stock and 3,215,000 shares of our Series D Convertible Preferred Stock, which we refer to as our Series D Preferred Stock, with an aggregate public offering price of \$80.0 million. Our common stock is listed on The Nasdaq Global Select Market under the symbol “SPRO.” On September 10, 2020, the last reported sale price for our common stock on The Nasdaq Global Select Market was \$11.12 per share. We do not intend to list our Series D Preferred Stock on any securities exchange or trading system.

The shares of Series D Preferred Stock are convertible on a one-to-one basis into shares of our common stock at any time at the option of the holder, provided that the holder will be prohibited from converting the Series D Preferred Stock into shares of our common stock if, as a result of such conversion, the holder, together with its affiliates, would own more than 9.99% of the total number of shares of our common stock then issued and outstanding. In the event of our liquidation, dissolution, or winding up, holders of our Series D Preferred Stock will receive a payment equal to \$0.001 per share of Series D Preferred Stock before any proceeds are distributed to the holders of our common stock. The Series D Preferred Stock has no voting rights, except as required by law and except that the consent of the Series D Preferred Stock holders will be required to amend the terms of the Series D Preferred Stock.

Investing in our common stock and our Series D Preferred Stock involves a high degree of risk. Please read “[Risk Factors](#)” on page S-6 of this prospectus supplement and under similar headings in the documents incorporated by reference into this prospectus supplement.

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

	<i>Per Share of Common Stock</i>	<i>Per Share of Series D Preferred Stock</i>	<i>Total</i>
Public offering price	\$ 10.00	\$ 10.00	\$80,000,000
Underwriting discounts and commissions(1)	\$ 0.60	\$ 0.60	\$ 4,800,000
Proceeds, before expenses, to us	\$ 9.40	\$ 9.40	\$75,200,000

(1) We have agreed to reimburse the underwriters for certain expenses. See “Underwriting.”

We have granted the underwriters an option for a period of 30 days from the date of this prospectus supplement to purchase up to an additional 1,200,000 shares of our common stock representing an aggregate public offering price of \$12.0 million. If the underwriters exercise the option in full, the total underwriting discounts and commissions payable by us will be \$5.5 million, and the total proceeds to us, before expenses, will be \$86.5 million. See “Underwriting” for more information.

The underwriters expect to deliver the securities to investors on or about September 15, 2020.

Joint Book-Running Managers

Cowen **Evercore ISI** **Cantor**

Lead Manager

Oppenheimer & Co.

Co-Manager

H.C. Wainwright & Co.

The date of this prospectus supplement is September 10, 2020.

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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 supplement and the accompanying 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 Series D Preferred Stock and also adds to and updates the information contained in the accompanying prospectus and the documents incorporated by reference into 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 and Series D Preferred Stock. Before buying any of the common stock or Series D Preferred 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”.

SPECIAL NOTE 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 and our cash runway;
- the timing and outcome of the New Drug Application approval process for tebipenem HBr;
- the initiation, timing, progress and results of, including interim data from, our preclinical studies and clinical trials, and our research and development programs;
- our ability to retain the continued service of our key professionals and to identify, hire and retain additional qualified professionals;
- our ability to advance product candidates into, and successfully complete, clinical trials;
- the timing or likelihood of regulatory filings and approvals;
- the direct and indirect impact of the pandemic caused by an outbreak of a new strain of coronavirus (“COVID-19”) on our business and operations, including manufacturing, research and development costs, clinical trials, regulatory processes and employee expenses;
- the commercialization of our product candidates, if approved;
- the pricing, coverage and reimbursement of our product candidates, if approved;
- the implementation of our business model, strategic plans for our business and product candidates;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates;
- 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.

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We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important cautionary statements in this prospectus and in the documents incorporated by reference in this prospectus, particularly in the “Risk Factors” section, that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. For a summary of such factors, please refer to the section entitled “Risk Factors” in this prospectus, as updated and supplemented by the discussion of risks and uncertainties under “Risk Factors” contained in any supplements to 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.

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 and Series D Preferred 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-6 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 treatments in high unmet need areas involving multi-drug resistant, or MDR, bacterial infections and rare diseases. Our most advanced product candidate, tebipenem pivoxil hydrobromide, or tebipenem HBr (previously SPR994), is designed to be the first oral carbapenem-class antibiotic for use in adults to treat MDR Gram-negative infections. Treatment with effective orally administrable antibiotics may prevent hospitalizations for serious infections and enable earlier, more convenient and cost-effective treatment of patients after hospitalization. We are also developing SPR720, a novel oral antibiotic designed for the treatment of non-tuberculous mycobacterial (NTM) disease, a rare, orphan disease caused by pulmonary non-tuberculous mycobacterial infections. In addition, we also have a platform technology known as our Potentiator Platform, that includes an IV-administered product candidate, SPR206, being developed to treat MDR Gram-negative infections in the hospital. We believe that our novel product candidates, if successfully developed and approved, would have a meaningful patient impact and significant commercial applications for the treatment of MDR infections in both the community and hospital settings.

Recent Developments

Tebipenem HBr—Positive Topline Results from Phase 3 ADAPT-PO Clinical Trial

On September 8, 2020, we announced positive topline results for the Phase 3 ADAPT-PO clinical trial of oral tebipenem HBr in complicated urinary tract infection (cUTI) and acute pyelonephritis (AP). The ADAPT-PO trial is the first ever trial to compare an all oral regimen against an all intravenous (IV) regimen for the treatment of cUTI. The pivotal Phase 3 clinical trial of oral tebipenem HBr met the primary endpoint, demonstrating statistical non-inferiority versus IV ertapenem. The primary endpoint of the trial was defined as the overall response rate (combined clinical cure plus microbiological eradication) at the test-of-cure (TOC) visit in the microbiological-intent-to-treat population (micro-ITT). Favorable overall response rates at TOC were 58.8% versus 61.6% for tebipenem HBr and ertapenem, respectively (treatment difference, -3.3%; 95% confidence interval [CI]: -9.7, 3.2; -12.5% NI margin). Clinical cure rates at TOC were high, at greater than 93% in both treatment groups, and overall response rates were consistent across key subgroups of interest.

In the ADAPT-PO trial, comparative safety data from the 1,372 hospitalized adult patients who enrolled in the trial suggest that tebipenem HBr was well-tolerated, with a safety profile similar to that of ertapenem. Treatment emergent adverse events (TEAEs) were reported in approximately 26% of patients in both treatment groups. The most commonly reported TEAEs in both treatment groups were diarrhea (5.0%) and headache (3.8%). Serious TEAEs were infrequent (1.3% for tebipenem HBr

versus 1.7% for ertapenem) and no deaths were reported in the trial. Three *Clostridiodes difficile*-associated TEAEs were observed in the ertapenem group, while none were observed in the tebipenem HBr group.

ADAPT-PO is a global, randomized, placebo-controlled Phase 3 clinical trial that evaluated the safety and efficacy of tebipenem HBr in hospitalized adult patients with cUTI or AP. Patients were randomized (1:1) to receive 600 mg of tebipenem HBr orally every 8 hours, or 1 g of ertapenem IV every 24 hours, for a total of 7 to 10 days. Patients with concurrent bacteremia received up to 14 days of therapy. The primary endpoint was the overall response, defined as the combination of clinical cure and microbiological eradication of the causative pathogen(s), at the TOC visit (Day 19, plus or minus 2 days) and was assessed in the micro-ITT population. The primary analysis and assessment of non-inferiority was evaluated using a pre-specified -12.5% non-inferiority (NI) margin. This NI margin was a modification of the original NI margin of -10% that was discussed with the U.S. Food and Drug Administration (FDA) because of concern that the COVID-19 pandemic could have an adverse effect on the trial. As a result, the NI margin was modified prior to database lock from the original NI margin. However, as noted by the lower bound of the 95% confidence interval (-9.7), the trial also achieved success according to the original -10% NI margin.

We plan to present emerging data from the tebipenem HBr program, including the ADAPT-PO clinical trial results, in detail at future scientific meetings and in publications. We intend to initiate a rolling New Drug Application (NDA) submission and anticipate completing the NDA submission to the FDA for tebipenem HBr in the second quarter of 2021.

SPR720—FDA Acceptance of IND Application

On August 31, 2020, we announced that the FDA accepted our investigational new drug (IND) application for SPR720. With the IND accepted, we expect to initiate a Phase 2a clinical trial evaluating SPR720 in patients with nontuberculous mycobacterial (NTM) pulmonary disease by year-end 2020. The planned Phase 2a clinical trial is designed as a multi-center, partially blinded, placebo-controlled proof-of-concept clinical trial that will enroll approximately 90 treatment-inexperienced patients with NTM pulmonary disease due to *Mycobacterium Avium complex*. Patients will be randomized to receive either 500mg or 1,000mg of oral SPR720, placebo or standard of care consisting of a macrolide and ethambutol, plus the option of adding a rifamycin. The objectives of the trial are to evaluate plasma pharmacokinetics, safety, tolerability, and microbiological response of SPR720 compared with placebo and standard of care over 28 days of treatment.

Corporate Information and History

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

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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

Common stock offered by us	4,785,000 shares.
Underwriters' option to purchase additional shares	We have granted the underwriters an option for a period of up to 30 days from the date of this prospectus supplement to purchase up to an additional 1,200,000 shares of common stock at the public offering price less the underwriting discounts and commissions.
Common stock to be outstanding immediately after this offering	25,799,095 shares (or 26,999,095 shares if the underwriters exercise their option to purchase additional shares in full).

Series D Convertible Preferred Stock

Series D Preferred Stock offered by us	3,215,000 shares.
Conversion	The shares of our Series D Preferred Stock are convertible on a one-to-one basis into shares of our common stock at any time at the option of the holder, provided that the holder will be prohibited from converting Series D Preferred Stock into shares of our common stock if, as a result of such conversion, the holder, together with its affiliates, would own more than 9.99% of the total number of shares of our common stock then issued and outstanding.
Liquidation preference	In the event of our liquidation, dissolution, or winding up, holders of our Series D Preferred Stock will receive a payment equal to \$0.001 per share of Series D Preferred Stock before any proceeds are distributed to the holders of our common stock.
Voting rights	Shares of Series D Preferred Stock will generally have no voting rights, except as required by law and except that the consent of the holders of the outstanding Series D Preferred Stock will be required to amend the terms of the Series D Preferred Stock.
Use of proceeds	We estimate that the net proceeds from this offering will be approximately \$74.8 million, or approximately \$86.1 million if the underwriters exercise their option to purchase additional shares in full, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

We intend to use the net proceeds from this offering, together with our existing cash and cash equivalents and committed funding from our existing BARDA contract and other non-dilutive funding commitments, to fund (i) the advancement of tebipenem HBr through the filing of a New Drug Application (NDA) with the U.S. Food and Drug Administration (FDA) and through the NDA approval process and (ii) the ongoing development of our pipeline products, and for working capital and other general corporate purposes. See "Use of Proceeds."

Risk factors

An investment in our securities involves a high degree of risk. See the information contained in or incorporated by reference under "Risk Factors" on page S-6 of this prospectus supplement and under similar headings in the other documents that are incorporated by reference herein and therein.

Nasdaq Global Select Market Symbol

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

The number of shares of common stock expected to be outstanding after this offering and, unless otherwise indicated, the information in this prospectus supplement are based on 21,014,095 shares of common stock outstanding as of June 30, 2020, and excludes:

- 1,720,000 shares of common stock issuable upon conversion of 1,720 outstanding shares of our Series A Convertible Preferred Stock as of June 30, 2020;
- 1,000,000 shares of common stock issuable upon conversion of 1,000 shares of our Series B Convertible Preferred Stock as of June 30, 2020;
- 2,287,000 shares of common stock issuable upon conversion of 2,287 shares of our Series C Convertible Preferred Stock as of June 30, 2020;
- 3,671,200 shares of common stock issuable upon exercise of outstanding options as of June 30, 2020, having a weighted average exercise price of \$8.54 per share, of which options to purchase 1,669,860 shares were vested as of such date;
- 30,561 shares of common stock issuable upon the vesting and release of outstanding restricted stock units as of June 30, 2020; and
- 973,465 shares of common stock reserved for future issuance as of June 30, 2020 under our 2017 Stock Incentive Plan, as amended, and our 2019 Inducement Equity Incentive Plan, as amended.

Except as otherwise indicated, we have presented the information in this prospectus supplement assuming:

- no exercise by the underwriters in this offering of their option to purchase additional shares; and
- no exercise of outstanding options described above.

RISK FACTORS

An investment in our securities involves a high degree of risk. Before deciding whether to invest in our securities, 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 securities 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

Management will have broad discretion as to the use of the net proceeds from this offering, and we may not use the proceeds effectively.

Our management will have broad discretion in the application of the net proceeds from this offering and could spend the proceeds in ways that do not improve our results of operations or enhance the value of our common stock. Our failure to apply these funds effectively could have a material adverse effect on our business, delay the development of our product candidates, and cause the price of our common stock to decline.

If you purchase securities in this offering, you will suffer immediate and substantial dilution.

If you purchase securities in this offering, you will incur immediate and substantial dilution in the as adjusted net tangible book value of the common stock that you purchase, or that is issuable upon conversion of the Series D Preferred Stock, of \$5.12 per share as of June 30, 2020, based on the public offering price of \$10.00 per share, because the price that you pay will be substantially greater than the net tangible book value per share of the shares you acquire. You will experience additional dilution upon the exercise of options, 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.

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 common stock or other securities convertible into or exchangeable for our shares of common stock at prices that may not be the same as the prices 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

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shareholders. The price per share at which we sell additional shares of common stock, or securities convertible or exchangeable into shares of common stock, in future transactions may be higher or lower than the prices 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.

Sales of a substantial number of our common stock by our existing shareholders in the public market could cause our stock price to fall.

If our existing shareholders sell, or indicate an intention to sell, substantial amounts of our common stock in the public market, the trading price of our common stock could decline. In addition, a substantial number of shares of common stock are subject to outstanding options or will become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules. If these additional shares of common stock are sold, or if it is perceived that they will be sold, in the public market, the trading price of our common stock could decline.

We, our executive officers and directors have agreed that, subject to certain exceptions, during the period ending 90 days after the date of this prospectus supplement, we and they will not offer, sell, contract to sell, pledge or otherwise dispose of, directly or indirectly, any of our common stock or securities convertible into or exchangeable or exercisable for any of our common stock, enter into a transaction that would have the same effect, or enter into any swap, hedge or other arrangement that transfers, in whole or in part, any of the economic consequences of ownership of our common stock, whether any of these transactions are to be settled by delivery of our common stock or other securities, in cash or otherwise, or publicly disclose the intention to make any offer, sale, pledge or disposition, or to enter into any transaction, swap, hedge or other arrangement, without, in each case, the prior written consent of Cowen and Company, LLC, Evercore Group L.L.C. and Cantor Fitzgerald & Co. Exceptions to the lock-up restrictions are described in more detail in this prospectus supplement under the caption "Underwriting."

Anti-takeover provisions in our charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our amended and restated certificate of incorporation, as amended, and amended and restated bylaws may delay or prevent an acquisition of us or a change in our management. These provisions include:

- authorizing the issuance of "blank check" preferred stock, the terms of which may be established and shares of which may be issued without stockholder approval;
- creating a staggered board of directors;
- prohibiting stockholder action by written consent, thereby requiring all stockholder actions to be taken at a meeting of our stockholders; and
- establishing advance notice requirements for nominations for election to the board of directors or for proposing matters that can be acted upon at stockholder meetings.

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In addition, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which limits the ability of stockholders owning in excess of 15% of our outstanding voting stock to merge or combine with us. Although we believe these provisions collectively provide for an opportunity to obtain greater value for stockholders by requiring potential acquirers to negotiate with our board of directors, they would apply even if an offer rejected by our board were considered beneficial by some stockholders. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors, which is responsible for appointing the members of our management.

USE OF PROCEEDS

We estimate that we will receive net proceeds of approximately \$74.8 (or approximately \$86.1 if the underwriters' option to purchase additional shares is exercised in full) from the sale of the shares of common stock and Series D Preferred Stock offered by us in this offering, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

We intend to use the net proceeds from this offering, together with our existing cash and cash equivalents and committed funding from our existing BARDA contract and other non-dilutive funding commitments, to fund (i) the advancement of tebipenem HBr through the filing of a New Drug Application (NDA) with the U.S. Food and Drug Administration (FDA) and through the NDA approval process and (ii) the ongoing development of our pipeline products, and for working capital and other general corporate purposes.

Although we currently 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 product development process, 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 factors described in "Risk Factors." Accordingly, our management will have broad discretion in applying the net proceeds from this offering. An investor will not have the opportunity to evaluate the economic, financial or other information on which we base our decisions on how to use the proceeds.

Based on our current plans, we believe that our existing cash and cash equivalents, together with the net proceeds from this offering and committed funding from our existing BARDA contract and other non-dilutive funding commitments, will be sufficient to enable us to fund our operating expenses and capital expenditure requirements into the first quarter of 2022, including through the filing of an NDA for tebipenem HBr and through the NDA approval process.

We have based this estimate on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect. We do not expect the net proceeds from this offering and our existing cash and cash equivalents to be sufficient to fund our operations to profitability or positive cash flows. We may satisfy our future cash needs through the sale of equity securities, debt financings, working capital lines of credit, corporate collaborations or license agreements, grant funding, interest income earned on invested cash balances or a combination of one or more of these sources.

Pending these uses, we intend to invest the net proceeds in high quality, investment grade instruments, certificates of deposit or direct or guaranteed obligations of the U.S. government, or hold such proceeds as cash.

CAPITALIZATION

The following table sets forth our cash and cash equivalents and capitalization as of June 30, 2020:

- on an actual basis; and
- on an as adjusted basis, giving effect to the sale of 4,785,000 shares of common stock by us in this offering and the sale of 3,215,000 shares of Series D Preferred Stock by us in this offering for aggregate net proceeds of \$74.8 million, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

	As of June 30, 2020	
	Actual	As Adjusted
	(dollars in thousands)	
Cash, cash equivalents and marketable securities	\$ 71,360	146,165
Stockholders' equity		
Common stock, \$0.001 par value; 60,000,000 shares authorized, 21,014,095 shares issued and outstanding, actual; 60,000,000 shares authorized, 25,799,095 issued and outstanding, as adjusted	\$ 21	\$ 26
Preferred stock, \$0.001 par value; 10,000,000 shares authorized, 5,007 shares issued and outstanding, actual; 10,000,000 shares authorized, 3,220,007 shares issued and outstanding, as adjusted	–	3
Additional paid-in capital	313,864	388,661
Accumulated deficit	(240,186)	(240,186)
Accumulated other comprehensive gain (loss)	15	15
Total stockholders' equity	73,714	148,519
Total capitalization	\$ 73,714	\$ 148,519

This table excludes:

- 1,720,000 shares of common stock issuable upon conversion of 1,720 outstanding shares of our Series A Convertible Preferred Stock as of June 30, 2020;
- 1,000,000 shares of common stock issuable upon conversion of 1,000 shares of our Series B Convertible Preferred Stock as of June 30, 2020;
- 2,287,000 shares of common stock issuable upon conversion of 2,287 shares of our Series C Convertible Preferred Stock as of June 30, 2020;
- 3,671,200 shares of common stock issuable upon exercise of outstanding options as of June 30, 2020, having a weighted average exercise price of \$8.54 per share, of which options to purchase 1,669,860 shares were vested as of such date;
- 30,561 shares of common stock issuable upon the vesting and release of outstanding restricted stock units as of June 30, 2020; and
- 973,465 shares of common stock reserved for future issuance as of June 30, 2020 under our 2017 Stock Incentive Plan, as amended, and our 2019 Inducement Equity Incentive Plan, as amended.

The above also assumes the following:

- no exercise by the underwriters in this offering of their option to purchase additional shares; and
- no exercise of outstanding options described above.

DILUTION

If you invest in our securities in this offering, your ownership interest will be diluted to the extent of the difference between the price per share you pay in this offering and the net tangible book value per share of our common stock immediately after this offering. The net tangible book value of our common stock as of June 30, 2020 was approximately \$73.7 million, or approximately \$3.51 per share of common stock based upon 21,014,095 shares outstanding as of June 30, 2020. Net tangible book value per share is equal to our total tangible assets, less our total liabilities, divided by the total number of shares outstanding. This discussion assumes that all purchasers in this offering elect to purchase common stock or to convert their shares of Series D Preferred Stock into common stock.

After giving effect to the sale by us of 4,785,000 shares of common stock at the public offering price of \$10.00 per share and 3,215,000 shares of Series D Preferred Stock at the public offering price of \$10.00 per share in this offering, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us, our net tangible book value as of June 30, 2020 would have been approximately \$148.5 million, or \$5.12 per share of common stock. This amount represents an immediate increase in net tangible book value of \$1.61 per share to existing stockholders and an immediate dilution of \$4.88 per share to purchasers in this offering. The following table illustrates the dilution:

Public offering price per share of common stock	\$ 10.00
Public offering price per share of preferred stock	\$ 10.00
Net tangible book value per share as of June 30, 2020	\$3.51
Increase per share attributable to new investors	\$1.61
As adjusted net tangible book value per share as of June 30, 2020, after giving effect to this offering	\$ 5.12
Dilution per share to new investors purchasing shares in this offering	\$ 4.88

The number of shares of common stock expected to be outstanding after this offering and, unless otherwise indicated, the information in this prospectus supplement are based on 21,014,095 shares of common stock outstanding as of June 30, 2020, and excludes:

- 1,720,000 shares of common stock issuable upon conversion of 1,720 outstanding shares of our Series A Convertible Preferred Stock as of June 30, 2020;
- 1,000,000 shares of common stock issuable upon conversion of 1,000 shares of our Series B Convertible Preferred Stock as of June 30, 2020;
- 2,287,000 shares of common stock issuable upon conversion of 2,287 shares of our Series C Convertible Preferred Stock as of June 30, 2020;
- 3,671,200 shares of common stock issuable upon exercise of outstanding options as of June 30, 2020, having a weighted average exercise price of \$8.54 per share, of which options to purchase 1,669,860 shares were vested as of such date;
- 30,561 shares of common stock issuable upon the vesting and release of outstanding restricted stock units as of June 30, 2020; and
- 973,465 shares of common stock reserved for future issuance as of June 30, 2020 under our 2017 Stock Incentive Plan, as amended, and our 2019 Inducement Equity Incentive Plan, as amended.

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The above also assumes the following:

- no exercise by the underwriters in this offering of their option to purchase additional shares; and
- no exercise of outstanding options described above.

If the underwriters exercise their option to purchase 1,200,000 shares of common stock in full, the as adjusted net tangible book value after this offering would be approximately 5.29 per share, representing an increase in net tangible book value of approximately \$1.78 per share to existing stockholders and immediate dilution in net tangible book value of approximately \$4.71 per share to investors purchasing our common stock in this offering at the public offering price.

DESCRIPTION OF SERIES D PREFERRED STOCK

Series D Preferred Stock

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

Rank. The shares of Series D Preferred Stock rank:

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

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

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

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

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After such preferential payment, each holder of shares of Series D 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 D Preferred Stock, including the Series A Preferred Stock, the Series B Preferred Stock and the Series C Preferred Stock, in the remaining distribution of the net assets of the Company available for distribution.

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

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

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

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

MATERIAL U.S. FEDERAL TAX CONSIDERATIONS FOR NON-U.S. HOLDERS

The following discussion is a summary of the material U.S. federal income tax considerations applicable to non-U.S. holders (as defined below) with respect to their ownership and disposition of shares of our common stock or Series D Preferred Stock issued pursuant to this offering. For purposes of this discussion, a “non-U.S. holder” means a beneficial owner of our common stock or Series D Preferred Stock that is for U.S. federal income tax purposes:

- a non-resident alien individual;
- a foreign corporation or any other foreign organization taxable as a corporation for U.S. federal income tax purposes;
- a foreign estate, the income of which is not subject to U.S. federal income tax on a net income basis; or
- a trust, (A) that does not have a valid election in effect under applicable United States Treasury regulations to be treated as a United States person, and (B) either (i) which is not subject to the primary supervision of a court within the United States, or (ii) for which one or more United States persons do not have the authority to control all substantial decisions.

This discussion does not address the tax treatment of partnerships or other entities that are pass-through entities for U.S. federal income tax purposes or persons that hold their common stock or Series D Preferred Stock through partnerships or other pass-through entities. A partner in a partnership or other pass-through entity that will hold our common stock or Series D Preferred Stock should consult his, her or its own tax advisor regarding the tax consequences of acquiring, holding and disposing of our common stock or Series D Preferred Stock through a partnership or other pass-through entity, as applicable.

This discussion is based on current provisions of the U.S. Internal Revenue Code of 1986, as amended, which we refer to as the Code, existing and proposed U.S. Treasury Regulations promulgated thereunder, current administrative rulings and judicial decisions, all as in effect as of the date of this prospectus supplement and, all of which are subject to change or to differing interpretation, possibly with retroactive effect. Any such change or differing interpretation could alter the tax consequences to non-U.S. holders described in this prospectus supplement. There can be no assurance that the Internal Revenue Service, which we refer to as the IRS, will not challenge one or more of the tax consequences described herein. We assume in this discussion that a non-U.S. holder holds shares of our common stock or Series D Preferred Stock as a capital asset within the meaning of Section 1221 of the Code (generally, property held for investment purposes).

This discussion does not address all aspects of U.S. federal income that may be relevant to a particular non-U.S. holder in light of that non-U.S. holder’s individual circumstances nor does it address any aspects of any U.S. state, local or non-U.S. taxes, the alternative minimum tax, any tax considerations resulting from a non-U.S. holder having a functional currency other than the U.S. dollar, the Medicare tax on net investment income, or any other U.S. federal tax other than the income tax. This discussion also does not consider any specific facts or circumstances that may apply to a non-U.S. holder and does not address the special tax rules applicable to particular non-U.S. holders, such as:

- insurance companies;
- tax exempt or governmental organizations;
- financial institutions;
- brokers or dealers in securities;

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- pension plans;
- “controlled foreign corporations,” “passive foreign investment companies,” and corporations that accumulate earnings to avoid U.S. federal income tax;
- “qualified foreign pension funds,” or entities wholly owned by a “qualified foreign pension fund”;
- persons deemed to sell our common stock or Series D Preferred Stock under the constructive sale provisions of the Code;
- persons that hold our common stock or Series D Preferred Stock as part of a straddle, hedge, conversion transaction, synthetic security or other integrated investment;
- persons who hold or receive our common stock or Series D Preferred Stock pursuant to the exercise of any employee stock option or otherwise as compensation;
- persons for whom our stock or Series D Preferred Stock constitutes “qualified small business stock” within the meaning of Section 1202 of the Code;
- persons subject to special tax accounting rules as a result of any item of gross income with respect to the stock being taken into account in an “applicable financial statement,” as defined in the Code; and
- certain U.S. expatriates.

This discussion is for general information only and is not tax advice. Accordingly, all prospective non-U.S. holders of our common stock or Series D Preferred Stock should consult their own tax advisors with respect to the U.S. federal, state, local and non-U.S. tax consequences of the purchase, ownership and disposition of our common stock or Series D Preferred Stock.

Distributions on Our Common Stock or Series D Preferred Stock

Distributions, if any, on our common stock or Series D Preferred Stock generally will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. If a distribution exceeds our current and accumulated earnings and profits, the excess will be treated as a tax-free return of the non-U.S. holder’s investment, up to such holder’s tax basis in the common stock or Series D Preferred Stock. Any remaining excess will be treated as capital gain, subject to the tax treatment described below in “Gain on Sale or Other Taxable Disposition of Our Common Stock or Series D Preferred Stock.” Any such distributions will also be subject to the discussion below under the sections titled “Backup Withholding and Information Reporting” and “Withholding and Information Reporting Requirements—FATCA.”

Subject to the discussion in the following two paragraphs in this section, dividends paid to a non-U.S. holder generally will be subject to withholding of U.S. federal income tax at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder’s country of residence.

Dividends that are treated as effectively connected with a trade or business conducted by a non-U.S. holder within the United States and, if an applicable income tax treaty so provides, that are attributable to a permanent establishment or a fixed base maintained by the non-U.S. holder within the United States, are generally exempt from the 30% withholding tax if the non-U.S. holder satisfies applicable certification and disclosure requirements. However, such U.S. effectively connected income, net of specified deductions and credits, is taxed at the same graduated U.S. federal income tax rates applicable to United States persons (as defined in the Code). Any U.S. effectively connected income received by a non-U.S. holder that is a corporation may also, under certain circumstances, be subject to an additional “branch profits tax” at a 30% rate or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder’s country of residence.

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A non-U.S. holder of our common stock or Series D Preferred Stock who claims the benefit of an applicable income tax treaty between the United States and such holder's country of residence generally will be required to provide a properly executed IRS Form W-8BEN or W-8BEN-E (or successor form) and satisfy applicable certification and other requirements. Non-U.S. holders are urged to consult their tax advisors regarding their entitlement to benefits under a relevant income tax treaty. A non-U.S. holder that is eligible for a reduced rate of U.S. withholding tax under an income tax treaty may obtain a refund or credit of any excess amounts withheld by timely filing a U.S. tax return with the IRS.

Gain on Sale or Other Taxable Disposition of Our Common Stock or Series D Preferred Stock

Subject to the discussion below under "Backup Withholding and Information Reporting" and "Withholding and Information Reporting Requirements—FATCA," a non-U.S. holder generally will not be subject to any U.S. federal income or withholding tax on any gain realized upon such holder's sale or other taxable disposition of shares of our common stock or Series D Preferred Stock unless:

- the gain is effectively connected with the non-U.S. holder's conduct of a U.S. trade or business and, if an applicable income tax treaty so provides, is attributable to a permanent establishment or a fixed-base maintained by such non-U.S. holder in the United States, in which case the non-U.S. holder generally will be taxed on a net income basis at the graduated U.S. federal income tax rates applicable to United States persons (as defined in the Code) and, if the non-U.S. holder is a foreign corporation, the branch profits tax described above in "Distributions on Our Common Stock or Series D Preferred Stock" also may apply;
- the non-U.S. holder is a nonresident alien individual who is present in the United States for 183 days or more in the taxable year of the disposition and certain other conditions are met, in which case the non-U.S. holder will be subject to a 30% tax (or such lower rate as may be specified by an applicable income tax treaty between the United States and such holder's country of residence) on the net gain derived from the disposition, which may be offset by certain U.S. source capital losses of the non-U.S. holder, if any (even though the individual is not considered a resident of the United States), provided that the non-U.S. holder has timely filed U.S. federal income tax returns with respect to such losses; or
- our common stock or Series D Preferred Stock, as applicable, constitutes a U.S. real property interest by reason of our status as a "U.S. real property holding corporation," or a USRPHC, for U.S. federal income tax purposes, at any time within the shorter of the five-year period preceding the disposition or the non-U.S. holder's holding period for our common stock or Series D Preferred Stock, as applicable. We believe we are not currently and do not anticipate becoming a USRPHC. However, because the determination of whether we are a USRPHC depends on the fair market value of our U.S. real property interests relative to the fair market value of our other business assets, there can be no assurance that we will not become a USRPHC in the future. Even if we become a USRPHC, however, gain arising from the sale or other taxable disposition by a non-U.S. holder of a class of our capital stock will not be subject to U.S. federal income tax as long as such class of stock is "regularly traded", as defined by applicable Treasury Regulations, on an established securities market and such non-U.S. holder does not, actually or constructively, hold more than five percent of such class of stock at any time during the applicable period that is specified in the Code. Our common stock is listed on The Nasdaq Global Select Market but we do not intend to list our Series D Preferred Stock on any securities exchange or trading system. If the foregoing exception does not apply, then if we are or were to become a USRPHC a purchaser may be required to withhold 15% of the proceeds payable to a non-U.S. holder from a sale of our common stock or Series D Preferred Stock, as applicable, and such non-U.S. holder generally will be subject to U.S. federal income tax on its net gain derived from the disposition at the graduated U.S. federal income tax rates applicable to United States persons (as defined in the Code).

Backup Withholding and Information Reporting

We must report annually to the IRS and to each non-U.S. holder the gross amount of the distributions on our common stock or Series D Preferred Stock paid to such holder and the tax withheld, if any, with respect to such distributions. Non-U.S. holders may have to comply with specific certification procedures to establish that the holder is not a United States person (as defined in the Code) in order to avoid backup withholding at the applicable rate, currently 24%, with respect to dividends on our common stock or Series D Preferred Stock. Dividends paid to non-U.S. holders subject to withholding of U.S. federal income tax, as described above in “Distributions on Our Common Stock or Series D Preferred Stock,” generally will be exempt from U.S. backup withholding.

Information reporting and backup withholding will generally apply to the proceeds of a disposition of our common stock or Series D Preferred Stock by a non-U.S. holder effected by or through the U.S. office of any broker, U.S. or foreign, unless the holder certifies its status as a non-U.S. holder and satisfies certain other requirements, or otherwise establishes an exemption. Generally, information reporting and backup withholding will not apply to a payment of disposition proceeds to a non-U.S. holder where the transaction is effected outside the United States through a non-U.S. office of a broker. However, for information reporting purposes, dispositions effected through a non-U.S. office of a broker with substantial U.S. ownership or operations generally will be treated in a manner similar to dispositions effected through a U.S. office of a broker. Non-U.S. holders should consult their own tax advisors regarding the application of the information reporting and backup withholding rules to them. Copies of information returns may be made available to the tax authorities of the country in which the non-U.S. holder resides or is incorporated under the provisions of a specific treaty or agreement. Backup withholding is not an additional tax. Any amounts withheld under the backup withholding rules from a payment to a non-U.S. holder can be refunded or credited against the non-U.S. holder’s U.S. federal income tax liability, if any, provided that an appropriate claim is filed with the IRS in a timely manner.

Withholding and Information Reporting Requirements—FATCA

The Foreign Account Tax Compliance Act, or FATCA, generally imposes a U.S. federal withholding tax at a rate of 30% on certain payments made to a foreign entity unless (i) if the foreign entity is a “foreign financial institution,” such foreign entity undertakes certain due diligence, reporting, withholding, and certification obligations, (ii) if the foreign entity is not a “foreign financial institution,” such foreign entity identifies certain of its U.S. investors, if any, or (iii) the foreign entity is otherwise exempt under FATCA.

Withholding under FATCA currently applies to dividends paid on our common stock or Series D Preferred Stock. The U.S. Treasury Department has released proposed regulations under FATCA providing for the elimination of the federal withholding tax of 30% applicable to gross proceeds of a sale or other disposition of our common stock or Series D Preferred Stock. Under these proposed U.S. Treasury Regulations (which may be relied upon by taxpayers prior to finalization), withholding under FATCA will not apply to gross proceeds from sales or other dispositions of our common stock or Series D Preferred Stock.

Non-U.S. holders should consult their tax advisors regarding the possible implications of this legislation on their investment in our securities and the entities through which they hold our securities, including, without limitation, the process and deadlines for meeting the applicable requirements to prevent the imposition of the 30% withholding tax under FATCA.

THE PRECEDING DISCUSSION OF U.S. FEDERAL TAX CONSIDERATIONS IS FOR GENERAL INFORMATION ONLY. IT IS NOT TAX ADVICE. EACH PROSPECTIVE INVESTOR SHOULD CONSULT ITS OWN TAX ADVISOR REGARDING THE PARTICULAR U.S. FEDERAL, STATE, LOCAL AND FOREIGN TAX CONSEQUENCES OF PURCHASING, HOLDING AND DISPOSING OF OUR SECURITIES, INCLUDING THE CONSEQUENCES OF ANY PROPOSED CHANGE IN APPLICABLE LAWS.

UNDERWRITING

Cowen and Company, LLC and Evercore Group L.L.C. are acting as representatives of each of the underwriters named below. Subject to the terms and conditions set forth in an underwriting agreement among us and the underwriters, we have agreed to sell to the underwriters, and each of the underwriters has agreed, severally and not jointly, to purchase from us, the number of shares of common stock and Series D Preferred Stock set forth opposite its name below.

Underwriter	Number of Shares of Common Stock	Number of Shares of Series D Preferred Stock
Cowen and Company, LLC	1,746,525	1,173,475
Evercore Group L.L.C.	1,459,425	980,575
Cantor Fitzgerald & Co.	957,000	643,000
Oppenheimer & Co. Inc.	406,725	273,275
H.C. Wainwright & Co., LLC	215,325	144,675
Total	4,785,000	3,215,000

Subject to the terms and conditions set forth in the underwriting agreement, the underwriters have agreed, severally and not jointly, to purchase all of the shares sold under the underwriting agreement if any of these shares are purchased. If an underwriter defaults, the underwriting agreement provides that the purchase commitments of the nondefaulting underwriters may be increased or the underwriting agreement may be terminated.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act, or to contribute to payments the underwriters may be required to make in respect of those liabilities and liabilities incurred in connection with the reserved share program described below.

The underwriters are offering the shares, subject to prior sale, when, as and if issued to and accepted by them, subject to approval of legal matters by their counsel, including the validity of the shares, and other conditions contained in the underwriting agreement, such as the receipt by the underwriters of officer's certificates and legal opinions. The underwriters reserve the right to withdraw, cancel or modify offers to the public and to reject orders in whole or in part.

Commissions and Discounts

The representatives have advised us that the underwriters propose initially to offer the shares to the public at the public offering price set forth on the cover page of this prospectus and to dealers at that price less a concession not in excess of \$0.36 per share. After the offering, the public offering price, concession or any other term of this offering may be changed.

The following table shows the public offering price, underwriting discount and proceeds before expenses to us. The information assumes either no exercise or full exercise by the underwriters of their option to purchase additional shares.

	Per Share of Common Stock	Per Share of Series D Preferred Stock	Without Option	With Option
Public offering price	10.00	10.00	80,000,000	92,000,000
Underwriting discount	0.60	0.60	4,800,000	5,520,000
Proceeds, before expenses, to us	9.40	9.40	75,200,000	86,480,000

The expenses of this offering, not including the underwriting discount, are estimated at \$0.4 million and are payable by us. We have agreed to reimburse the underwriters for certain of their expenses in an amount up to \$25,000.

Option to Purchase Additional Shares

We have granted an option to the underwriters, exercisable for 30 days after the date of this prospectus, to purchase up to 1,200,000 additional shares of common stock at the public offering price, less the underwriting discount. If the underwriters exercise this option, each will be obligated, subject to conditions contained in the underwriting agreement, to purchase a number of additional shares proportionate to that underwriter's initial amount reflected in the above table.

No Sales of Similar Securities

We, our executive officers and directors have agreed not to sell or transfer any common stock or securities convertible into, exchangeable for, exercisable for, or repayable with common stock, including the Series D Preferred Stock, for 90 days after the date of this prospectus without first obtaining the written consent of Cowen and Company, LLC and Evercore Group L.L.C. Specifically, we and these other persons have agreed, with certain limited exceptions, not to directly or indirectly:

- offer, pledge, sell or contract to sell any common stock,
- sell any option or contract to purchase any common stock,
- purchase any option or contract to sell any common stock,
- grant any option, right or warrant for the sale of any common stock,
- lend or otherwise dispose of or transfer any common stock,
- request or demand that we file a registration statement related to the common stock, or
- enter into any swap or other agreement that transfers, in whole or in part, the economic consequence of ownership of any common stock whether any such swap or transaction is to be settled by delivery of shares or other securities, in cash or otherwise.

The foregoing restrictions are subject to certain limited exceptions, including sales by executive officers pursuant to Rule 10b5-1 trading plans in effect as of the date hereof.

This lock-up provision applies to common stock and to securities convertible into or exchangeable or exercisable for or repayable with common stock, including the Series D Preferred Stock owned now or acquired later by the person executing the agreement or for which the person executing the agreement later acquires the power of disposition.

Nasdaq Global Select Market Listing

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

Price Stabilization, Short Positions and Penalty Bids

In connection with this offering, the underwriters may engage in stabilizing transactions, which involves making bids for, purchasing and selling shares of common stock in the open market for the purpose of preventing or retarding a decline in the market price of our common stock while this offering is in progress. These stabilizing transactions may include making short sales of the common stock, which involves the sale by the underwriters of a greater number of shares of common stock than they are required to purchase in this offering, and purchasing shares of common stock in the open market to cover positions created by short sales. Short sales may be "covered" shorts, which are short positions in an amount not greater than the underwriters' option to purchase additional shares referred to above, or may be "naked" shorts, which are short positions in excess of that amount. The underwriters may close out any covered short position either by exercising their option to purchase additional shares, in whole or in part, or by purchasing shares in the open market. In making this determination, the underwriters will consider, among other things, the price of shares available for purchase in the open market compared to the price at which the underwriters may purchase shares through the option to purchase additional shares. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of our common stock in the open market that could adversely affect investors who purchase in this offering. To the extent that the underwriters create a naked short position, they will purchase shares in the open market to cover the position.

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The underwriters have advised us that, pursuant to Regulation M of the Securities Act, they may also engage in other activities that stabilize, maintain or otherwise affect the price of our common stock, including the imposition of penalty bids. This means that if the representatives of the underwriters purchase common stock in the open market in stabilizing transactions or to cover short sales, the representatives can require the underwriters that sold those shares as part of this offering to repay the underwriting discount received by them.

In addition, in connection with this offering, the underwriters may engage in passive market making transactions in our common stock on The Nasdaq Global Select Market prior to the pricing and completion of this offering. Passive market making consists of displaying bids on The Nasdaq Global Select Market no higher than the bid prices of independent market makers and making purchases at prices no higher than these independent bids and effected in response to order flow. Net purchases by a passive market maker on each day are generally limited to a specified percentage of the passive market maker's average daily trading volume in the common stock during a specified period and must be discontinued when such limit is reached. Passive market making may cause the price of our common stock to be higher than the price that otherwise would exist in the open market in the absence of these transactions. If passive market making is commenced, it may be discontinued at any time.

These activities may have the effect of raising or maintaining the market price of our common stock or preventing or retarding a decline in the market price of our common stock, and, as a result, the price of our common stock may be higher than the price that otherwise might exist in the open market. If the underwriters commence these activities, they may discontinue them at any time. The underwriters may carry out these transactions on The Nasdaq Global Select Market, in the over-the-counter market or otherwise.

Neither we nor any of the underwriters make any representation or prediction as to the direction or magnitude of any effect that the transactions described above may have on the price of our common stock. In addition, neither we nor any of the underwriters make any representation that the representatives will engage in these transactions or that these transactions, once commenced, will not be discontinued without notice.

Electronic Distribution

In connection with this offering, certain of the underwriters or securities dealers may distribute prospectuses by electronic means, such as emails.

Other Relationships

Some of the underwriters and their affiliates have engaged in, and may in the future engage in, investment banking and other commercial dealings in the ordinary course of business with us or our affiliates. They have received, or may in the future receive, customary fees and commissions for these transactions.

In addition, in the ordinary course of their business activities, the underwriters and their affiliates may make or hold a broad array of investments and actively trade debt and equity securities (or related derivative securities) and financial instruments (including bank loans) for their own account and for the accounts of their customers. Such investments and securities activities may involve securities and/or instruments of ours or our affiliates. The underwriters and their affiliates may also make investment recommendations and/or publish or express independent research views in respect of such securities or financial instruments and may hold, or recommend to clients that they acquire, long and/or short positions in such securities and instruments.

We are party to a sales agreement with Cantor, pursuant to which we may sell up to \$50.0 million of our common stock from time to time through an "at-the-market" offering program. As of the date of

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this prospectus supplement, we have sold \$15.4 million of our common stock pursuant to the sales agreement and the prospectus underlying this “at-the-market” offering program has been terminated.

Selling Restrictions

European Economic Area and the United Kingdom

In relation to each Member State of the European Economic Area and the United Kingdom (each a “Relevant State”), no Shares have been offered or will be offered pursuant to the Offering to the public in that Relevant State prior to the publication of a prospectus in relation to the Shares which has been approved by the competent authority in that Relevant State or, where appropriate, approved in another Relevant State and notified to the competent authority in that Relevant State, all in accordance with the Prospectus Regulation, except that offers of Shares may be made to the public in that Relevant State at any time under the following exemptions under the Prospectus Regulation:

- a. to any legal entity which is a qualified investor as defined under the Prospectus Regulation;
- b. to fewer than 150 natural or legal persons (other than qualified investors as defined under the Prospectus Regulation), subject to obtaining the prior consent of representatives for any such offer; or
- c. in any other circumstances falling within Article 1(4) of the Prospectus Regulation,

provided that no such offer of Shares shall require the Issuer or any Manager to publish a prospectus pursuant to Article 3 of the Prospectus Regulation or supplement a prospectus pursuant to Article 23 of the Prospectus Regulation.

Each person in a Relevant State who initially acquires any Shares or to whom any offer is made will be deemed to have represented, acknowledged and agreed to and with the Company and the Managers that it is a qualified investor within the meaning of the Prospectus Regulation.

In the case of any Shares being offered to a financial intermediary as that term is used in Article 5(1) of the Prospectus Regulation, each such financial intermediary will be deemed to have represented, acknowledged and agreed that the Shares acquired by it in the offer have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in circumstances which may give rise to an offer to the public other than their offer or resale in a Relevant State to qualified investors, in circumstances in which the prior consent of the underwriters has been obtained to each such proposed offer or resale.

The Company, the underwriters and their affiliates will rely upon the truth and accuracy of the foregoing representations, acknowledgements and agreements.

For the purposes of this provision, the expression an “offer to the public” in relation to any Shares in any Relevant State means the communication in any form and by any means of sufficient information on the terms of the offer and any Shares to be offered so as to enable an investor to decide to purchase or subscribe for any Shares, and the expression “Prospectus Regulation” means Regulation (EU) 2017/1129.

References to the Prospectus Regulation includes, in relation to the UK, the Prospectus Regulation as it forms part of UK domestic law by virtue of the European Union (Withdrawal) Act 2018.

The above selling restriction is in addition to any other selling restrictions set out below.

Notice to Prospective Investors in the United Kingdom

This document is for distribution only to persons who (i) have professional experience in matters relating to investments and who qualify as investment professionals within the meaning of Article 19(5)

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of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (as amended, the “Financial Promotion Order”), (ii) are persons falling within Article 49(2)(a) to (d) (“high net worth companies, unincorporated associations etc.”) of the Financial Promotion Order, (iii) are outside the United Kingdom, or (iv) are persons to whom an invitation or inducement to engage in investment activity (within the meaning of Section 21 of the Financial Services and Markets Act 2000, as amended (“FSMA”)) in connection with the issue or sale of any securities may otherwise lawfully be communicated or caused to be communicated (all such persons together being referred to as “relevant persons”). This document is directed only at relevant persons and must not be acted on or relied on by persons who are not relevant persons. Any investment or investment activity to which this document relates is available only to relevant persons and will be engaged in only with relevant persons.

Notice to Prospective Investors in Switzerland

This prospectus supplement is not intended to constitute an offer or solicitation to purchase or invest in the shares. The shares may not be publicly offered, directly or indirectly, in Switzerland within the meaning of the Swiss Financial Services Act (“FinSA”) and no application has or will be made to admit the shares to trading on any trading venue (exchange or multilateral trading facility) in Switzerland. Neither this prospectus supplement nor any other offering or marketing material relating to the shares constitutes a prospectus pursuant to the FinSA, and neither this prospectus supplement nor any other offering or marketing material relating to the shares may be publicly distributed or otherwise made publicly available in Switzerland.

Notice to Prospective Investors in the Dubai International Financial Centre

This prospectus supplement relates to an Exempt Offer in accordance with the Offered Securities Rules of the Dubai Financial Services Authority (“DFSA”). This prospectus supplement is intended for distribution only to persons of a type specified in the Offered Securities Rules of the DFSA. It must not be delivered to, or relied on by, any other person. The DFSA has no responsibility for reviewing or verifying any documents in connection with Exempt Offers. The DFSA has not approved this prospectus nor taken steps to verify the information set forth herein and has no responsibility for the prospectus supplement. The shares to which this prospectus supplement relates may be illiquid and/or subject to restrictions on their resale. Prospective purchasers of the shares offered should conduct their own due diligence on the shares. If you do not understand the contents of this prospectus supplement you should consult an authorized financial advisor.

Notice to Prospective Investors in Australia

No placement document, prospectus, product disclosure statement or other disclosure document has been lodged with the Australian Securities and Investments Commission (“ASIC”), in relation to the offering. This prospectus supplement does not constitute a prospectus, product disclosure statement or other disclosure document under the Corporations Act 2001 (the “Corporations Act”), and does not purport to include the information required for a prospectus, product disclosure statement or other disclosure document under the Corporations Act.

Any offer in Australia of the shares may only be made to persons (the “Exempt Investors”) who are “sophisticated investors” (within the meaning of section 708(8) of the Corporations Act), “professional investors” (within the meaning of section 708(11) of the Corporations Act) or otherwise pursuant to one or more exemptions contained in section 708 of the Corporations Act so that it is lawful to offer the shares without disclosure to investors under Chapter 6D of the Corporations Act.

The shares applied for by Exempt Investors in Australia must not be offered for sale in Australia in the period of 12 months after the date of allotment under the offering, except in circumstances where disclosure to investors under Chapter 6D of the Corporations Act would not be required pursuant to an exemption under section 708 of the Corporations Act or otherwise or where the offer is pursuant to a

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disclosure document which complies with Chapter 6D of the Corporations Act. Any person acquiring shares must observe such Australian on-sale restrictions.

This prospectus supplement contains general information only and does not take account of the investment objectives, financial situation or particular needs of any particular person. It does not contain any securities recommendations or financial product advice. Before making an investment decision, investors need to consider whether the information in this prospectus supplement is appropriate to their needs, objectives and circumstances, and, if necessary, seek expert advice on those matters.

Notice to Prospective Investors in Hong Kong

The shares have not been offered or sold and will not be offered or sold in Hong Kong, by means of any document, other than (a) to “professional investors” as defined in the Securities and Futures Ordinance (Cap. 571) of Hong Kong and any rules made under that Ordinance; or (b) in other circumstances which do not result in the document being a “prospectus” as defined in the Companies Ordinance (Cap. 32) of Hong Kong or which do not constitute an offer to the public within the meaning of that Ordinance. No advertisement, invitation or document relating to the shares has been or may be issued or has been or may be in the possession of any person for the purposes of issue, whether in Hong Kong or elsewhere, which is directed at, or the contents of which are likely to be accessed or read by, the public of Hong Kong (except if permitted to do so under the securities laws of Hong Kong) other than with respect to shares which are or are intended to be disposed of only to persons outside Hong Kong or only to “professional investors” as defined in the Securities and Futures Ordinance and any rules made under that Ordinance.

Notice to Prospective Investors in Japan

The shares have not been and will not be registered under the Financial Instruments and Exchange Law of Japan (Law No. 25 of 1948, as amended) and, accordingly, will not be offered or sold, directly or indirectly, in Japan, or for the benefit of any Japanese Person or to others for re-offering or resale, directly or indirectly, in Japan or to any Japanese Person, except in compliance with all applicable laws, regulations and ministerial guidelines promulgated by relevant Japanese governmental or regulatory authorities in effect at the relevant time. For the purposes of this paragraph, “Japanese Person” shall mean any person resident in Japan, including any corporation or other entity organized under the laws of Japan.

Notice to Prospective Investors in Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, the shares were not offered or sold or caused to be made the subject of an invitation for subscription or purchase and will not be offered or sold or caused to be made the subject of an invitation for subscription or purchase, and this prospectus or any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the shares, has not been circulated or distributed, nor will it be circulated or distributed, whether directly or indirectly, to any person in Singapore other than (i) to an institutional investor (as defined in Section 4A of the Securities and Futures Act (Chapter 289) of Singapore, as modified or amended from time to time (the “SFA”)) pursuant to Section 274 of the SFA, (ii) to a relevant person (as defined in Section 275(2) of the SFA) pursuant to Section 275(1) of the SFA, or any person pursuant to Section 275(1A) of the SFA, and in accordance with the conditions specified in Section 275 of the SFA, or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

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Where the shares are subscribed or purchased under Section 275 of the SFA by a relevant person which is:

- (a) a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor; or
- (b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor,

securities or securities-based derivatives contracts (each term as defined in Section 2(1) of the SFA) of that corporation or the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the shares pursuant to an offer made under Section 275 of the SFA except:

- (a) to an institutional investor or to a relevant person, or to any person arising from an offer referred to in Section 275(1A) or Section 276(4)(i)(B) of the SFA;
- (b) where no consideration is or will be given for the transfer;
- (c) where the transfer is by operation of law; or
- (d) as specified in Section 276(7) of the SFA.

Notice to Prospective Investors in Canada

The shares may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 *Prospectus Exemptions* or subsection 73.3(1) of the *Securities Act* (Ontario), and are permitted clients, as defined in National Instrument 31-103 *Registration Requirements, Exemptions and Ongoing Registrant Obligations*. Any resale of the shares must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus supplement (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 (or, in the case of securities issued or guaranteed by the government of a non-Canadian jurisdiction, section 3A.4) of National Instrument 33-105 *Underwriting Conflicts* (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

Notice to Prospective Investors in Israel

In the State of Israel this prospectus supplement shall not be regarded as an offer to the public to purchase shares of common stock under the Israeli Securities Law, 5728 – 1968, which requires a prospectus to be published and authorized by the Israel Securities Authority, if it complies with certain provisions of Section 15 of the Israeli Securities Law, 5728 – 1968, including, inter alia, if: (i) the offer is made, distributed or directed to not more than 35 investors, subject to certain conditions (the "Addressed Investors"); or (ii) the offer is made, distributed or directed to certain qualified investors defined in the First Addendum of the Israeli Securities Law, 5728 – 1968, subject to certain conditions (the "Qualified Investors"). The Qualified Investors shall not be taken into account in the count of the Addressed Investors and may be offered to purchase securities in addition to the 35 Addressed Investors. The company has not and will not take any action that would require it to publish a

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prospectus in accordance with and subject to the Israeli Securities Law, 5728 – 1968. We have not and will not distribute this prospectus or make, distribute or direct an offer to subscribe for our common stock to any person within the State of Israel, other than to Qualified Investors and up to 35 Addressed Investors.

Qualified Investors may have to submit written evidence that they meet the definitions set out in of the First Addendum to the Israeli Securities Law, 5728 – 1968. In particular, we may request, as a condition to be offered common stock, that Qualified Investors will each represent, warrant and certify to us and/or to anyone acting on our behalf: (i) that it is an investor falling within one of the categories listed in the First Addendum to the Israeli Securities Law, 5728 – 1968; (ii) which of the categories listed in the First Addendum to the Israeli Securities Law, 5728 – 1968 regarding Qualified Investors is applicable to it; (iii) that it will abide by all provisions set forth in the Israeli Securities Law, 5728 – 1968 and the regulations promulgated thereunder in connection with the offer to be issued common stock; (iv) that the shares of common stock that it will be issued are, subject to exemptions available under the Israeli Securities Law, 5728 – 1968: (a) for its own account; (b) for investment purposes only; and (c) not issued with a view to resale within the State of Israel, other than in accordance with the provisions of the Israeli Securities Law, 5728 – 1968; and (v) that it is willing to provide further evidence of its Qualified Investor status. Addressed Investors may have to submit written evidence in respect of their identity and may have to sign and submit a declaration containing, inter alia, the Addressed Investor's name, address and passport number or Israeli identification number.

LEGAL MATTERS

The validity of the securities offered by this prospectus will be passed upon for us by Mintz, Levin, Cohn, Ferris, Glovsky & Popeo, P.C., Boston, Massachusetts. Certain legal matters in connection with this offering will be passed upon for the underwriters by Latham & Watkins LLP.

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, 2019 have been so incorporated in reliance on the report (which contains an explanatory paragraph related to substantial doubt about the Company's ability to continue as a going concern, as described in Note 1 to the consolidated financial statements) of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

WHERE YOU CAN FIND ADDITIONAL 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.

INCORPORATION OF CERTAIN INFORMATION 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 year ended December 31, 2019, filed with the SEC on March 16, 2020;
- our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2020 and June 30, 2020, filed with the SEC on [May 8, 2020](#) and [August 6, 2020](#), respectively;
- our Current Reports on Form 8-K (and amendments thereto), filed with the SEC on [January 30, 2020](#), [February 11, 2020](#), [February 28, 2020](#), [April 16, 2020](#) (as amended by the Current Report Form 8-K/A filed with the SEC on [May 11, 2020](#)), [June 4, 2020](#), [September 8, 2020](#) and [September 9, 2020](#) (except for the information furnished under Items 2.02 or 7.01 and the exhibits furnished thereto);
- the description of our common stock contained in our Registration Statement on [Form 8-A](#) initially filed on October 30, 2017, including any amendment or report filed for the purpose of updating such description; and
- all reports and other documents subsequently filed by us (other than current reports furnished under Item 2.02 or Item 7.01 of Form 8-K and exhibits filed on such form that are related to such items) 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. We are not, however, incorporating by reference any documents or portions thereof, whether specifically listed above or filed in the future, that are not deemed “filed” with the SEC, including any information furnished pursuant to Items 2.02 or 7.01 of Form 8-K or related exhibits furnished pursuant to Item 9.01 of Form 8-K.

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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 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.

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 depository 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.

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.



4,785,000 Shares of Common Stock

3,215,000 Shares of Series D Convertible Preferred Stock

PROSPECTUS SUPPLEMENT

Cowen

Evercore ISI

Cantor

Oppenheimer & Co.

H.C. Wainwright & Co.

September 10, 2020.
