

**PROSPECTUS SUPPLEMENT  
(To Prospectus dated December 3, 2018)**



**Up to 3,333,333 Shares of Common Stock  
Up to 3,333 Shares of Series C Convertible Preferred Stock**

We are conducting a rights offering pursuant to which we are distributing to holders of our common stock and Series A Convertible Preferred Stock ("Series A Preferred Stock") and Series B Convertible Preferred Stock ("Series B Preferred Stock"), at no charge, non-transferable subscription rights to purchase shares of our common stock and Series C Convertible Preferred Stock ("Series C Preferred Stock"), with an aggregate offering value of \$30,000,000. For each share of common stock (including shares of common stock issuable upon conversion of the Company's outstanding shares of Series A Preferred Stock and Series B Preferred Stock) for which you are the holder of record as of 5:00 p.m., New York time, on February 10, 2020, you will receive 0.152 rights to purchase shares of our common stock (subject to the aggregate offering threshold and certain ownership limitations). Each whole right will allow you to subscribe for one share of common stock at the subscription price (or an equivalent number of shares of Series C Preferred Stock) on the terms described in this prospectus supplement.

The total number of subscription rights issued to each stockholder will be rounded down to the nearest whole number. Each subscription right will entitle you to purchase a portion of one share of our common stock at a subscription price equal to \$9.00 per whole share.

Any participant in the rights offering that, following exercise of such participant's subscription right would be or become a holder of greater than 9.99% of the outstanding number of shares of our common stock following the offering may elect to instead purchase Series C Preferred Stock at a purchase price of \$9,000 per share (ratably adjusted for fractional shares), and any such holder so electing would have a right to purchase one one-thousandth of a share of Series C Preferred Stock for each share of common stock it had a right to purchase under the subscription rights. Each share of Series C Preferred Stock will be convertible into 1,000 shares of common stock at the election of the holder, subject to beneficial ownership conversion limits applicable to the Series C Preferred Stock. The Series C Preferred Stock will generally have no voting rights, except as required by law, and will participate *pari passu* (on an as-converted basis) with any distribution of proceeds to holders of common stock and Series A Preferred Stock and Series B Preferred Stock, in the event of the Company's liquidation, dissolution or winding up or the payment of a dividend on the common stock.

The subscription rights may be exercised at any time during the subscription period, which will commence on February 11, 2020. The subscription rights will expire if they are not exercised by 5:00 p.m., New York time, on March 2, 2020, unless we extend the rights offering period. We reserve the right to extend the rights offering period at our sole discretion, subject to certain limitations described herein. Following the expiration of the offering period, we will offer funds managed by BVF Partners L.P. ("BVF"), and/or its transferee(s) or assignee(s), the opportunity to subscribe for the remaining portion (if any) of shares offered but not sold hereunder (the "Remaining Shares"), with the total gross offering proceeds not to exceed \$30,000,000. BVF may elect to purchase the Remaining Shares in any combination of common stock and/or Series C Preferred Stock, as permitted by applicable Nasdaq rules. This right is separate from the BVF Backstop Commitment pursuant to the Investment Agreement described below. You should carefully consider whether to exercise your subscription rights before the expiration of the rights offering period. All exercises of subscription rights are irrevocable. Our Board of Directors is making no recommendation regarding your exercise of the subscription rights. The subscription rights may not be sold, transferred or assigned to anyone else and will not be listed for trading on any stock exchange or market.

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The shares of common stock and Series C Preferred Stock are being offered directly by us without the services of an underwriter or selling agent.

We have separately entered into an Investment Agreement with BVF pursuant to which BVF has agreed to purchase from us a number of shares of Series C Preferred Stock with an aggregate value equal to the unsubscribed portion (if any) of the securities offered by this prospectus supplement that remains following the expiration of the offering period and following the expiration of BVF's right to purchase some or all of the Remaining Shares. See "Description of the Backstop Commitment."

We reserve the right to cancel the rights offering at any time for any reason. If we cancel the rights offering, all subscription payments received by the subscription agent, who is our transfer agent, will be returned, without interest or penalty, as soon as practicable.

Our common stock is traded on The Nasdaq Global Select Market under the symbol "SPRO." On February 10, 2020, the last reported sales price of our common stock on The Nasdaq Global Select Market was \$10.33 per share.

The exercise of your subscription rights for shares of our common stock involves risks. You should carefully consider all of the information set forth in this prospectus supplement and the accompanying prospectus, including the risk factors beginning on page S-15 of this prospectus supplement as well as the risk factors and other information in any documents we incorporate by reference into this prospectus supplement and the accompanying prospectus before exercising your subscription rights. See "Where You Can Find More Information" and "Incorporation by Reference."

**An investment in our common stock and Series C Preferred Stock involves risks. Before making an investment decision, you should carefully review the information under "Risk Factors" beginning on page S-15 of this prospectus supplement and in our Annual Report on Form 10-K for the fiscal year ended December 31, 2018 and our Quarterly Reports on Form 10-Q for the quarterly periods ended subsequent to our filing of such Annual Report, each of which has been filed with the Securities and Exchange Commission and each of which is incorporated by reference in this prospectus supplement and the accompanying prospectus.**

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

**The date of this prospectus supplement is February 11, 2020**

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**We have not authorized anyone to provide any information or to make any representations other than those contained in or incorporated by reference into this prospectus supplement, the accompanying prospectus or in any free writing prospectuses prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus supplement relates only to the subscription rights and underlying shares offered hereby, but only under circumstances and in jurisdictions where it is lawful to make such an offer. The information contained in or incorporated by reference into this prospectus supplement or the accompanying prospectus is accurate only as of its date regardless of the time of delivery of this prospectus supplement or of any distribution of subscription rights or sale of securities.**

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 filed with the Securities and

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Exchange Commission (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 a document incorporated by reference is inconsistent with a statement in another document incorporated by reference having a later date, the statement in the document having the later date modifies or supersedes the earlier statement.

Persons who come into possession of this prospectus supplement, the accompanying prospectus and any free writing prospectus in jurisdictions outside the United States are required to inform themselves about and to observe any restrictions as to this offering and the distribution of this prospectus supplement, the accompanying prospectus and any free writing prospectus applicable to that jurisdiction.

This prospectus supplement and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus contain market data and industry statistics and forecasts that are based on independent industry publications and other publicly available information. Although we believe that these sources are reliable, we do not guarantee the accuracy or completeness of this information and we have not independently verified this information. Although we are not aware of any misstatements regarding the market and industry data presented or incorporated by reference into this prospectus supplement and the accompanying prospectus, these estimates involve risks and uncertainties and are subject to change based on various factors, including those discussed under the heading “Risk Factors” and any related free writing prospectus. Accordingly, investors should not place undue reliance on this information.

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

## QUESTIONS AND ANSWERS RELATING TO THE RIGHTS OFFERING

### What is being offered in this rights offering?

We are distributing at no charge to holders of our common stock and Series A Preferred Stock and Series B Preferred Stock non-transferable subscription rights to purchase shares of our common stock. For each share of common stock (including shares of common stock issuable upon conversion of the Company's outstanding shares of Series A Preferred Stock and Series B Preferred Stock) for which you are the holder of record as of 5:00 p.m., New York time, on February 10, 2020, you will receive 0.152 rights to purchase shares of our common stock (subject to the aggregate offering threshold and certain ownership limitations). Each whole right will allow you to subscribe for one share of common stock at the subscription price (or an equivalent number of shares of Series C Preferred Stock) on the terms described in this prospectus supplement. The subscription rights entitle the holders to purchase up to an aggregate of approximately 3,333,333 shares of common stock (or an equivalent number of shares of Series C Preferred Stock). The subscription rights will be evidenced by subscription rights certificates.

The total number of subscription rights issued to each stockholder will be rounded down to the nearest whole number. Each subscription right will entitle you to purchase one share of our common stock at a subscription price equal to \$9.00 per share. Because the total number of subscription rights issued to each stockholder will be rounded down to the nearest whole number, we may not issue the full number of shares authorized for issuance in connection with this rights offering. Any excess subscription payments received by the subscription agent will be returned, without interest or penalty, as soon as practicable.

### What are the subscription rights?

For each whole right that you own, you will have the right to buy from us one share of our common stock at the subscription price. You may exercise some or all of your subscription rights, or you may choose not to exercise any subscription rights.

For example, if you owned 10,000 shares of our common stock as of 5:00 p.m., New York time, on the record date, you would receive subscription rights representing the right to purchase 1,520 shares of common stock for \$9.00 per share.

### Why are we conducting the rights offering?

We are conducting the rights offering in order to raise additional capital and to improve and strengthen our financial position. We intend to use the net proceeds from the rights offering, together with our existing cash, cash equivalents and marketable securities and committed funding from our BARDA contract and other non-dilutive funding commitments, to fund the advancement of tepipenem HBr and the initiation of a Phase 2a clinical trial of SPR720 and the remainder for working capital and other general corporate purposes. See "Use of Proceeds."

In authorizing the rights offering, our Board of Directors considered and evaluated a number of factors, including:

- our current capital resources and our future need for additional liquidity and capital;
- the size and timing of the rights offering;
- the potential dilution to our current stockholders if they choose not to participate in the rights offering;
- alternatives available for raising capital, including debt and other forms of equity raises;
- the potential impact of the rights offering on the public float for our common stock;
- BVF's willingness to backstop the rights offering;

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- that applicable Nasdaq marketplace rules do not require stockholder approval of the rights offering or the Backstop Commitment (as defined below); and
- the fact that existing stockholders would have the opportunity to participate on *apro rata* basis to purchase additional shares of common stock.

### **How was the subscription price for the rights offering determined?**

Our Board of Directors considered a number of factors in determining the price for the rights offering, including:

- the price per share at which BVF is willing to backstop the rights offering;
- “pass through” savings as a result of conducting the rights offering with no investment banking support;
- the price at which our stockholders might be willing to participate in the rights offering;
- historical and current trading prices for our common stock, including on a volume weighted average share price basis over certain periods; and
- the desire to provide an opportunity to our stockholders to participate in the rights offering on *apro rata* basis.

### **What is the role of BVF in this offering?**

Following the expiration of the offering period, we will offer funds managed by BVF the opportunity to subscribe for the remaining portion (if any) of shares offered but not sold hereunder (the “Remaining Shares”), with the total gross offering proceeds not to exceed \$30,000,000.

Separately, BVF has agreed to purchase a number of shares of Series C Preferred Stock with an aggregate value equal to the remaining unsubscribed portion of the securities offered by this prospectus supplement. This purchase commitment is set forth in a separate Investment Agreement, which would provide for the purchase of these shares (if applicable) in a private placement that is exempt from registration under Section 4(a)(2) of the Securities Act of 1933 (the “Backstop Commitment”). The purchase of the shares under the Backstop Commitment would be at the same price at which securities are offered hereunder. BVF will not receive a fee in connection with the Backstop Commitment; however, we have agreed to reimburse up to \$50,000 of BVF’s reasonable legal fees and expenses in connection with the Investment Agreement and the rights offering.

### **Am I required to exercise the rights I receive in the rights offering?**

No. You may exercise any number of your subscription rights, or you may choose not to exercise any subscription rights. However, if you choose not to fully exercise your rights and other stockholders fully exercise their subscription rights and/or BVF acquires the Remaining Shares hereunder or acquires shares of Series C Preferred Stock pursuant to the Backstop Commitment, the percentage of our common stock (including shares issuable upon conversion of shares of preferred stock) owned by other stockholders will increase, the relative percentage of our common stock that you own will decrease, and your voting and other rights may be diluted.

### **Has our Board of Directors made a recommendation to our stockholders regarding the rights offering?**

Our Board of Directors is making no recommendations regarding your exercise of the subscription rights. Stockholders who exercise subscription rights risk investment loss on new money invested. We cannot assure you that the trading price for our common stock will be above the subscription price at the time of exercise or at the expiration of the rights offering period or that anyone purchasing shares at the subscription price will be able to sell those shares in the future at the same price or a higher price. You are urged to make your own decision whether or not to exercise your subscription rights based on your own assessment of our business and the rights offering. See “Risk Factors” in this prospectus supplement and in the documents incorporated by reference into this prospectus supplement and the accompanying prospectus.

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**Who may participate in the rights offering?**

All stockholders of record, including holders of Series A Preferred Stock and Series B Preferred Stock on a non-converted basis, as of 5:00 p.m., New York time, on February 10, 2020, the record date approved by our Board of Directors for this rights offering, are entitled to receive rights and purchase shares in this rights offering.

**Will our directors, executive officers or significant stockholders participate in the rights offering?**

Our directors and executive officers who own shares of common stock, as well as other significant stockholders, are permitted, but not required, to participate in the rights offering on the same terms and conditions applicable to all stockholders in the rights offering. Certain of our directors, executive officers and significant stockholders may participate in the rights offering. There is no assurance that any of such parties will purchase shares in the rights offering. BVF has expressed its intention to purchase its *pro rata* share in the rights offering and has also committed to purchase shares of our Series C Preferred Stock in an amount equal to the aggregate value of the shares of common stock (if any) not subscribed for in the rights offering, pursuant to the Backstop Commitment.

**How soon must I act to exercise my subscription rights?**

The subscription rights may be exercised at any time during the subscription period, which commences on February 11, 2020, through the expiration date for the rights offering, which is 5:00 p.m., New York time, on March 2, 2020. If you elect to exercise any subscription rights, the subscription agent must actually receive all required documents and payments from you at or prior to the expiration date. Although we have the option of extending the expiration date of the subscription period at our sole discretion, we currently do not intend to do so.

**May I transfer my subscription rights?**

No, the rights are exercisable only by stockholders of record as of the record date, and you may not sell, transfer or assign your subscription rights to anyone else.

**Are there any limits on the number of shares of common stock I may own as a result of the exercise of subscription rights under the rights offering?**

Yes. You may only purchase the number of whole shares of common stock purchasable upon exercise of the rights distributed to you in the rights offering. Accordingly, the number of shares of common stock that you may purchase in the rights offering is limited by the number of our shares of common stock you held (including any shares of common stock issuable upon the exercise of Series A Preferred Stock and Series B Preferred Stock) on the record date. Additionally, if, immediately following the exercise of your subscription rights, you would beneficially own more than 9.99% of the total number of shares of the Company's common stock issued and outstanding immediately after the issuance of such shares, you may elect to receive shares of Series C Preferred Stock (at a subscription price of \$9,000 per whole share of Series C Preferred Stock) rather than shares of common stock. We reserve the right to reject any or all subscriptions not properly submitted or the acceptance of which would, in the opinion of our counsel, be unlawful.

**Are we requiring a minimum subscription to complete the rights offering?**

No. Any shares not subscribed for in the rights offering may be purchased by BVF as part of its right to purchase the Remaining Shares. To the extent that the total subscriptions in the rights offering (including through BVF's purchase of any portion of the Remaining Shares) does not equal \$30,000,000, then such shortfall will be purchased by BVF pursuant to the Backstop Commitment as shares of Series C Preferred Stock.

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**Are there any other conditions to the completion of the rights offering?**

Yes. The completion of the rights offering is subject to the conditions described under “Description of the Rights Offering—Amendment, Withdrawal and Termination.”

**Can the rights offering be canceled?**

Yes. We reserve the right to cancel the rights offering at any time for any reason. If the rights offering is canceled, all subscription payments received by the subscription agent will be returned, without interest or penalty, as soon as practicable to those persons who subscribed for shares in the rights offering.

**How do I exercise my subscription rights if I am a record holder of shares of common stock?**

If you wish to participate in the rights offering, you must properly complete the subscription rights certificate distributed by the subscription agent and deliver it, along with the full subscription price, to the subscription agent before 5:00 p.m., New York time, on March 2, 2020. If you use the mail, we recommend that you use insured, registered mail, return receipt requested.

If you send a payment that is insufficient to purchase the number of shares you requested, or if the number of shares you requested is not specified in the forms, the payment received will be applied to exercise your subscription rights to the fullest extent possible based on the amount of the payment received. If the payment exceeds the subscription price for the full exercise of your subscription rights, then the excess will be returned to you as soon as practicable. You will not receive interest on any payments refunded to you under the rights offering.

**What should I do if I want to participate in the rights offering, but my shares are held in the name of my broker, dealer, custodian bank or other nominee?**

If you hold your shares of common stock in “street name” through a broker, dealer, custodian bank or other nominee, you will not receive an actual subscription rights certificate. Instead, as described in this prospectus supplement, you must instruct your broker, dealer, custodian bank or other nominee whether or not to exercise rights on your behalf. We will ask your broker, dealer, custodian bank or other nominee to notify you of the rights offering.

If you wish to participate in the rights offering, you should complete and return to your nominee the form entitled “Beneficial Owner Election Form.” You should receive this form from your nominee with the other rights offering materials. If your shares are held in the name of a broker, dealer or other nominee, then you should send your subscription payment to that nominee as well pursuant to their instructions. You must act timely to ensure that your broker, dealer, custodian bank or other nominee acts for you and that all required forms and payments are actually received by the subscription agent prior to the expiration of the rights offering period.

**If the rights offering is not completed, will my subscription payment be refunded to me?**

Yes. The subscription agent will hold all funds it receives in a segregated bank account until completion of the rights offering. If the rights offering is not completed, the subscription agent will return, without interest or penalty, as soon as practicable, all subscription payments. If you own shares in “street name,” it may take longer for you to receive payment because the payments will be returned through your nominee.

**Must I pay the subscription price in cash?**

Yes. You must timely pay the full subscription price for the full number of shares of common stock you wish to acquire in the rights offering by personal check that clears before the expiration date of the rights offering.

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**Will the shares of common stock I acquire in the rights offering be subject to any stockholder agreement restricting my ability to sell or transfer my new shares of common stock?**

No. You will not be subject to any stockholder agreement that restricts your ability to sell or transfer any new shares of common stock acquired by you in the rights offering. However, under federal securities laws, our affiliates will be subject to restrictions on their ability to transfer shares of our common stock by virtue of their status as “affiliates” of us. An “affiliate” is generally defined as a person that directly, or indirectly through one or more intermediaries, controls or is controlled by, or is under common control with, us.

**After I exercise my subscription rights, may I change my mind?**

No. All exercises of subscription rights are irrevocable by the stockholders, even if you later learn information about us that you consider unfavorable or our stock price declines. You should not exercise your subscription rights unless you are certain that you wish to purchase the shares of common stock offered pursuant to this rights offering. However, we may cancel, extend or otherwise amend the rights offering at any time prior to the expiration date.

**Does exercising my subscription rights involve risk?**

Yes. The exercise of your subscription rights involves risks. Exercising your subscription rights involves the purchase of additional shares of our common stock and should be considered as carefully as you would consider other equity investments. Among other things, you should carefully consider the risks described under the heading “Risk Factors” in this prospectus supplement and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus.

**What fees or charges apply if I exercise my subscription rights?**

We are not charging any fees or sales commissions to issue subscription rights to you or to issue shares to you if you exercise your subscription rights. If you exercise your subscription rights through a broker or other record holder of your shares, you are responsible for paying any fees that person or entity may charge.

**When will I receive my new shares of common stock?**

Unless otherwise requested, all shares of common stock that you purchase in the rights offering will be issued in book-entry, or uncertificated, form. All shares of Series C Preferred Stock will be certificated. When issued, the shares will be registered in the name of the subscription rights holder of record. As soon as practicable after the expiration of the rights offering, the subscription agent will arrange for the issuance of the shares of common stock purchased pursuant in the rights offering. Subject to state securities laws and regulations, we have the discretion to delay distribution of any shares you may have elected to purchase by exercise of your subscription rights in order to comply with state securities laws.

**What are the material U.S. federal income tax consequences of the receipt and exercise of my subscription rights?**

For U.S. federal income tax purposes, we do not believe you should recognize income or loss in connection with the receipt or exercise of subscription rights in the rights offering, but the treatment of the receipt and exercise of subscription rights is unclear in certain respects. You are urged to consult your own tax advisor as to your particular tax consequences resulting from the receipt and exercise of subscription rights and the receipt, ownership and disposition of our common stock. For further information, please see “Material U.S. Federal Income Tax Consequences to U.S. Holders.”

**What happens if I choose not to exercise my subscription rights?**

You are not required to exercise your subscription rights or otherwise take any action in response to this rights offering. If you do not exercise your subscription rights, and the rights offering is completed, the number of

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shares of our common stock you own will not change but, due to the fact that shares will be purchased by other stockholders in the rights offering and/or BVF, your percentage ownership of our total outstanding common stock will decrease, and your voting and other rights will be diluted.

### **How many shares of common stock will be outstanding after the rights offering?**

As of the record date, there were 19,282,091 shares of our common stock outstanding, not including 2,720,000 shares of our common stock issuable upon the conversion of 2,720 shares of our Series A Preferred Stock and Series B Preferred Stock outstanding as of the record date. We will issue up to a maximum of 3,333,333 shares of common stock (or an equivalent number of shares of Series C Preferred Stock) in the rights offering and/or pursuant to the Backstop Commitment. Based on the number of shares issued and outstanding as of the record date, if we issue all 3,333,333 shares of common stock available in this rights offering, we would have 22,615,424 shares of common stock issued and outstanding following the completion of the rights offering, not including 2,720,000 shares of our common stock issuable upon the conversion of 2,720 shares of our Series A Preferred Stock and Series B Preferred Stock outstanding as of the record date.

### **How much money will we receive from the rights offering and related financing?**

If we issue all 3,333,333 shares of common stock (or an equivalent number of shares of Series C Preferred Stock) available in this rights offering, we will receive gross proceeds of \$30,000,000. The net proceeds to us, after deducting estimated offering expenses, will be approximately \$29.5 million. We estimate that the expenses of the rights offering will be approximately \$0.5 million. We are conducting the rights offering in order to raise additional capital and to improve and strengthen our financial position. If any portion of the securities offered herein is not purchased in the rights offering, then BVF has committed to purchase a number of shares of Series C Preferred Stock with an aggregate value equal to such shortfall.

We intend to use the net proceeds from the rights offering, together with our existing cash, cash equivalents and marketable securities and committed funding from our BARDA contract and other non-dilutive funding commitments, to fund the advancement of tebipenem HBr and the initiation of a Phase 2a clinical trial of SPR720 and the remainder for working capital and other general corporate purposes. See "Use of Proceeds."

### **Who should I contact if I have more questions?**

If you have more questions about the rights offering process or need additional copies of the rights offering documents, please contact our information agent, Alliance Advisors LLC, at 200 Broadacres Drive, 3rd Floor, Bloomfield, NJ 07003, 800-574-6215 or [reorg@allianceadvisorsllc.com](mailto:reorg@allianceadvisorsllc.com).

## PROSPECTUS SUPPLEMENT SUMMARY

*This summary highlights the information contained elsewhere in or incorporated by reference into this prospectus supplement and the accompanying prospectus. This summary does not contain all of the information that you should consider before deciding whether to exercise your subscription rights. You should carefully read this entire prospectus supplement, including the information under the heading “Risk Factors,” and the documents incorporated by reference into this prospectus supplement and the accompanying prospectus, which are described under the headings “Where You Can Find More Information” and “Incorporation by Reference.”*

You should rely only on the information contained in this prospectus supplement and the accompanying prospectus. We have not authorized anyone to provide you with information different from the information contained in this prospectus supplement or the accompanying prospectus. The subscription rights, common stock and Series C Preferred Stock are not being offered in any jurisdiction where offers and sales are not permitted. The information contained in this prospectus supplement is accurate only as of the date of this prospectus supplement, regardless of when this prospectus supplement is delivered or when any sale of our securities occurs.

### Our Company and Corporate History

#### 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 recommendation from independent data review committee regarding pivotal Phase 3 clinical trial and exercise of \$15.9 million option by BARDA for tebipenem HBr development***

On October 3, 2019, we announced that an independent review committee evaluated interim pharmacokinetic plasma data following the first 70 patients enrolled in our ongoing ADAPT-PO pivotal Phase 3 clinical trial of tebipenem HBr, our oral carbapenem product candidate, and recommended that we continue the trial without modification of the protocol-defined dose. The independent review committee reviewed interim plasma concentration data from the first 33 patients who were randomized to tebipenem HBr in the Phase 3 clinical trial for the treatment of complicated urinary tract infections, or cUTI, and acute pyelonephritis, or AP. A primary objective of the independent review committee was to confirm that plasma levels of tebipenem HBr in patients in the Phase 3 clinical trial support the selected treatment dose. The Phase 3 trial remains blinded and will continue as planned. ADAPT-PO is designed as a double-blind, double-dummy clinical trial to compare oral tebipenem HBr dosed as 600 mg administered three times per day, or TID, with a standard of care IV-administered antibiotic, ertapenem, in approximately 1,200 patients with cUTI or AP, randomized 1:1 in each arm. We expect to report top-line data from the Phase 3 clinical trial in the third quarter of 2020.

On February 5, 2020, we announced that the Biomedical Advanced Research and Development Authority (BARDA) exercised its first contract option for additional committed funding pursuant to its existing contract with Spero. Specifically, the option exercise provides Spero with \$15.9 million in reimbursement for the further development of tebipenem HBr. The \$15.9 million option exercise is expected to support the funding of specified manufacturing activities required for approval of tebipenem HBr including active pharmaceutical ingredient, or API, validation batch manufacturing and stability studies. Additionally, the option is expected to support the funding of several non-clinical and clinical development activities including a Phase 1 bronchoalveolar lavage, or BAL, study in healthy subjects that we anticipate initiating in the third quarter of 2020, as well as non-human primate efficacy studies in one or more models of biothreat disease. The option was exercised under Spero's existing 2018 contract with BARDA, which provides for reimbursement to Spero of up to \$46.8 million for qualified expenses for tebipenem HBr development over a five-year period. Total committed funding under the BARDA award to date is \$34.1 million, inclusive of this first contract option being exercised. There is a second option exercisable by BARDA for the remaining \$12.6 million of funding, subject to specified milestones being achieved under the award agreement. Furthermore, the Defense Threat Reduction Agency (DTRA) provides up to \$10.0 million, in addition to the total potential award from BARDA, to cover the cost of the nonclinical biodefense aspects of the collaboration program for tebipenem HBr.

***SPR720—First indication of human safety and PK profiles for SPR720 supports advancement of program to a Phase 2 proof-of-concept clinical trial in patients planned to initiate in the second half of 2020***

On December 4, 2019, we announced preliminary findings from our Phase 1 first-in-human clinical trial of SPR720. Analysis of blinded data from the Phase 1 double-blind, placebo-controlled single ascending dose, or SAD, and multiple ascending dose, or MAD, clinical trial in healthy volunteers suggests that SPR720 is generally well-tolerated, with a pharmacokinetic profile that we believe supports the further development of SPR720 as an oral agent for the treatment of NTM disease. Specifically, there were no serious adverse events reported and all participants completed the trial. An analysis of preliminary data indicates that SPR720 was generally well-tolerated at doses up to 1000 mg over the maximum studied duration of 14 days. Preliminary analyses of PK data across the cohorts show no significant impact of either advanced age or administration with food on PK variables. At doses of 500 mg or higher, the mean plasma drug exposures of SPR719, the active metabolite of SPR720, are consistent with those suggested by *in vitro* and *in vivo* models of SPR720 to be necessary for clinical efficacy against target NTM pathogens. In early February 2020 the SPR720 Phase 1 clinical trial was unblinded and the findings are in line with the preliminary analysis. We plan to submit an Investigational New Drug Application, or IND, to the FDA and initiate a Phase 2a clinical trial of SPR720 in patients with NTM disease during the second half of 2020.

***Potentiator Platform—Based on preliminary findings from Phase 1 clinical trial, Spero selects SPR206 as lead product candidate within Potentiator Platform, and discontinues development of SPR741***

On January 13, 2020, we announced preliminary findings from our Phase 1 first-in-humans clinical trial of SPR206, an IV-administered product candidate being developed by Spero as an innovative option to treat MDR Gram-negative bacterial infections. Analysis of preliminary, blinded data from the Phase 1 double-blind, placebo-controlled SAD and MAD clinical trial in healthy adult volunteers suggests that SPR206 is well-tolerated at doses that are likely to be within a therapeutic range for target MDR Gram-negative bacterial infections and has a safety profile that we believe supports the further development of SPR206. The decision to continue development of SPR206 is also supported by data from nonclinical studies in which SPR206 demonstrated activity as a single agent against MDR and extensively drug resistant, or XDR, bacterial strains, including isolates of *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and carbapenem-resistant *Enterobacteriaceae*, in both *in vitro* and *in vivo* models of infection.

The Phase 1 clinical trial of SPR206 (Study SPR206-101) evaluated the safety, tolerability and pharmacokinetics of intravenously administered SPR206 at single doses ranging from 10 mg to 400 mg in seven SAD cohorts and

repeat total daily doses ranging from 75 mg to 450 mg for seven consecutive days and 300 mg for 14 consecutive days across five MAD cohorts. A total of 96 healthy volunteers were randomized to receive SPR206 or placebo. All reported adverse events were mild to moderate and there were no reported severe or serious adverse events. No evidence of nephrotoxicity was observed and there were no subjects with clinically significant changes in laboratory tests during the study. Although the data remain blinded, an analysis of preliminary data indicates that SPR206 was well-tolerated at doses up to 100 mg administered three-times a day, a total of 300 mg daily, for 14 consecutive days. Preliminary analyses of pharmacokinetic data across the cohorts indicates dose linearity and dose proportionality as well as mean plasma drug exposures of SPR206 that are concordant with preclinical models predictive for clinical efficacy against target Gram-negative pathogens.

We expect to receive a development milestone payment from our partner Everest Medicines upon delivery of the SPR206-101 SAD/MAD clinical study report, or CSR, as specified under the regional collaboration launched in 2019 and expects to present final data from the Phase 1 clinical trial in the first half of 2020. In conjunction with Everest Medicines, and through its grant from the U.S. Department of Defense awarded in July 2019, Spero plans to conduct a Phase 1 BAL clinical trial assessing the penetration of SPR206 into the pulmonary compartment in the second half of 2020 as well as initiate a renal impairment study of SPR206.

Based on the foregoing, we have determined to discontinue development of SPR741, effective January 1, 2020. We believe that the collective data from the recent Phase 1 and preclinical studies suggest a potency and safety profile for SPR206 that may be superior to SPR741. Further, we believe SPR206 may have a potentially faster path to pivotal clinical trials when compared with SPR741 because SPR206 is being developed as a single agent. As a result of this decision, we have terminated our license agreement with Northern Antibiotics Oy (Ltd.) relating to SPR741. Effective January 1, 2020, the intellectual property rights associated with SPR741 have entirely reverted to Northern Antibiotics and we no longer have any rights with respect thereto and we no longer have any obligations for the cost of maintaining such intellectual property.

***Preliminary Estimate of Cash Balance as of December 31, 2019, Updated Cash Runway Statement and Our Ability to Continue as a Going Concern***

As of December 31, 2019, our preliminary estimate of cash, cash equivalents and marketable securities was approximately \$82.0 million. Based on our current plans, we believe that our existing cash, cash equivalents and marketable securities, together with committed funding from our existing BARDA contract and other non-dilutive funding commitments, will be sufficient to fund our operating expenses and capital expenditure requirements into the fourth quarter of 2020, including through top-line data readout of our pivotal Phase 3 clinical trial of tebipenem HBr. Together with the net proceeds from this offering, based on our current plans, we expect these funds to be sufficient to fund our operating expenses and capital expenditure requirements into the first quarter of 2021, including through the filing of an NDA for tebipenem HBr.

In accordance with Accounting Standards Update (“ASU”) 2014-15, Disclosure of Uncertainties about an Entity’s Ability to Continue as a Going Concern (Subtopic 205-40), we are required to evaluate whether there are conditions and events, considered in the aggregate, that raise substantial doubt about our ability to continue as a going concern from the issuance date of our financial statements. Because our funds currently on hand and the expected net proceeds from this offering will not be sufficient to fund our operations, as currently planned, for more than one year beyond the filing date of this prospectus supplement, we have determined that there is substantial doubt regarding our ability to continue as a going concern. In connection with our future filing of our Annual Report on Form 10-K for the year ended December 31, 2019 (Form 10-K), we expect that we will disclose in such filing that we will not have sufficient liquidity to fund our operations for more than one year beyond the filing date of the Form 10-K. As a result, we expect that the opinion from our independent registered public accounting firm on such annual financial statements will contain an explanatory paragraph about such substantial doubt about our ability to continue as a going concern. We will require additional funding to fund the

development of our product candidates through regulatory approval and commercialization, and to support our continued operations. There is no assurance that we will be successful in obtaining sufficient funding on acceptable terms, if at all, and we could be forced to delay, reduce or eliminate some or all of our research and development programs, product portfolio expansion or commercialization efforts, which could materially adversely affect our business prospects or our ability to continue operations.

Our estimated cash, cash equivalents and marketable securities as of December 31, 2019 are preliminary and may change, are based on information available to management as of the date of this prospectus supplement, and are subject to completion by management of our financial statements as of and for the year ended December 31, 2019. There can be no assurance that our cash, cash equivalents and marketable securities as of December 31, 2019 will not differ from these estimates and any such changes could be material. The preliminary financial data included in this prospectus supplement has been prepared by, and is the responsibility of, our management. PricewaterhouseCoopers LLP has not audited, reviewed, compiled or applied agreed-upon procedures with respect to the preliminary financial data. Accordingly, PricewaterhouseCoopers LLP does not express an opinion or any other form of assurance with respect thereto. Complete year-end results will be included in our Annual Report on Form 10-K for the year ended December 31, 2019.

### **Corporate Information**

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

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

The mark “Spero Therapeutics” is our common law trademark. All other service marks, trademarks and trade names appearing in this prospectus are the property of their respective owners. We do not intend our use or display of other companies’ trade names, trademarks or service marks to imply a relationship with, or an endorsement or sponsorship of us by, these other companies. Solely for convenience, trademarks and tradenames referred to in this prospectus may appear without the ® or ™ 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 Rights Offering**

Securities Offered

We are distributing at no charge non-transferable subscription rights for each share of common stock (including shares of common stock issuable upon conversion of our outstanding shares of Series A Preferred Stock and Series B Preferred Stock) outstanding as of 5:00 p.m., New York time, on February 10, 2020. The total number of subscription rights issued to each holder will be rounded down to the nearest whole number. As a result, we may not issue the full number of shares authorized for issuance in connection with the rights offering.

Any participant in the rights offering that, immediately following exercise of its subscription right would be or become a holder of greater than 9.99% of the outstanding number of shares of our common stock following the offering may elect to instead purchase shares of our Series C Preferred Stock. We intend to sell the Series C Preferred Stock at \$9,000 per share, and any such holder so electing would have a right to purchase one one-thousandth of a share of Series C Preferred Stock for each share of common stock it had a right to purchase under the subscription rights. Each share of Series C Preferred Stock will, subject to certain limitations, be convertible into 1,000 shares of common stock at the election of the holder. The Series C Preferred Stock will generally have no voting rights, except as required by law, and will participate pari passu with any distribution of proceeds to holders of common stock and Series A Preferred Stock and Series B Preferred Stock in the event of our liquidation, dissolution or winding up or the payment of a dividend on the common stock.

Subscription Right

For each share of common stock (including shares of common stock issuable upon conversion of the Company's outstanding shares of Series A Preferred Stock and Series B Preferred Stock), we will distribute 0.152 rights to purchase shares of our common stock (subject to the aggregate offering threshold and certain ownership limitations). The total number of subscription rights issued will be rounded down to the nearest whole number. Each whole right will allow its holder to subscribe for one share of common stock at the subscription price (or an equivalent number of shares of Series C Preferred Stock on the terms described in this prospectus supplement). Holders may exercise some or all of their subscription rights, or may choose not to exercise their subscription rights.

Subscription Price

The subscription price per share of common stock is \$9.00. To be effective, any payment related to the exercise of a subscription right must be received and must clear prior to the expiration of the rights offering period.

Record Date

February 10, 2020.

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Use of Proceeds	We intend to use the net proceeds from the rights offering, together with our existing cash, cash equivalents and marketable securities and committed funding from our BARDA contract and other non-dilutive funding commitments, to fund the advancement of tebipenem HBr and the initiation of a Phase 2a clinical trial of SPR720 and the remainder for working capital and other general corporate purposes.
Procedure for Exercising Subscription Rights	The subscription rights may be exercised at any time during the subscription period, which commences on February 11, 2020. If you are a holder of record, to exercise your subscription rights, you must properly complete the subscription rights certificate distributed by the subscription agent and deliver it, along with the full subscription price, to the subscription agent, Computershare Trust Company, N.A. before 5:00 p.m., New York time, on March 2, 2020, unless the expiration date is extended. If your shares are held in the name of a broker, dealer, custodian bank or other nominee, you must provide instructions to that broker, dealer, custodian bank or other nominee.
Payment Adjustments	If you send a payment that is insufficient to purchase the number of shares requested, or if the number of shares requested is not specified in the subscription rights certificate, the payment received will be applied to exercise your subscription rights to the extent of the payment. If the payment exceeds the amount necessary for the full exercise of your subscription rights, the excess will be returned to you as soon as practicable. You will not receive interest or any penalty on any payments refunded to you under the rights offering.
Shares of Common Stock Issued and Outstanding Before the Rights Offering, Eligible to Participate in the Rights Offering and Outstanding After Completion of the Rights Offering	<p>As of the record date, there were 19,282,091 shares of our common stock outstanding, 1,720 shares of our Series A Preferred Stock outstanding, and 1,000 shares of our Series B Preferred Stock outstanding.</p> <p>We will issue up to an aggregate of 3,333,333 shares of common stock (or the number of shares of Series C Preferred Stock which may be converted into that number of shares of common stock in the rights offering). To the extent that this number of shares (on an actual or as-converted basis) is not issued in the rights offering, then we expect that the shortfall would be issued to BVF pursuant to the Backstop Commitment. Based on the number of shares outstanding as of the record date, if we issue all 3,333,333 shares of common stock (or an equivalent number of shares of Series C Preferred Stock) available in this rights offering and/or pursuant to the Backstop Commitment, we would have 22,615,424 shares of common stock (measured on an as-converted basis) issued and outstanding following the completion of the rights offering, which does not include 2,720,000 shares of our</p>

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	<p>common stock issuable upon the conversion of our Series A Preferred Stock and Series B Preferred Stock outstanding as of the record date.</p>
Subscription Ratio	<p>Based on an aggregate of 22,002,091 shares outstanding as of the record date or deemed to be outstanding (assuming conversion of all Series A Preferred Stock and Series B Preferred Stock) each share of common stock (including common stock issuable upon the conversion of Series A Preferred Stock and Series B Preferred Stock) held of record (or deemed to be held) as of the record date will receive 0.152 rights to purchase shares of our common stock (subject to the aggregate offering threshold and certain ownership limitations). Each whole right will allow its holder to subscribe for one share of common stock at the subscription price (or an equivalent number of shares of Series C Preferred Stock on the terms described in this prospectus supplement). To the extent that any portion of the rights remain unexercised following the expiration of the offering period, BVF will have the right to purchase up to the full amount of the unsubscribed shares.</p>
Non-transferability of Subscription Rights	<p>The subscription rights may not be sold, transferred or assigned to anyone else.</p>
Backstop Commitment	<p>We have entered into an Investment Agreement with BVF, pursuant to which BVF has agreed to purchase from us, subject to certain conditions, shares of Series C Preferred Stock in an amount equal to the aggregate value of the shares of common stock not subscribed for in the rights offering, at a price per share equal to \$9,000 per share (the “Backstop Commitment”). BVF will not receive a fee in connection with the Backstop Commitment; however, we have agreed to reimburse up to \$50,000 of BVF’s reasonable legal fees and expenses in connection with the Investment Agreement and the rights offering.</p>
No Revocation of Exercise by Stockholders	<p>All exercises of subscription rights are irrevocable, even if you later learn information about us that you consider unfavorable or our stock price declines. You should not exercise your subscription rights unless you are certain that you wish to purchase the shares of common stock offered pursuant to this rights offering.</p>
Conditions to the Rights Offering	<p>The completion of the rights offering is subject to the conditions described under “Description of the Rights Offering—Amendment, Withdrawal and Termination.”</p>
Amendment; Cancellation	<p>We may amend the terms of the rights offering or extend the rights offering period and we reserve the right to cancel the rights offering at any time prior to the expiration date for any reason. If the rights offering is cancelled, all subscription payments received by the</p>

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	<p>subscription agent will be returned, without interest or penalty, as soon as practicable, to those persons who subscribed for shares in the rights offering. We will notify you of any amendments or modifications to the terms of the rights offering, or if the rights offering is cancelled, by issuing a press release.</p>
No Board Recommendation	<p>Our Board of Directors is making no recommendations regarding your exercise of the subscription rights. You are urged to make your own decision whether or not to exercise your subscription rights based on your own assessment of our business and the rights offering. See “Risk Factors.”</p>
Issuance of Stock	<p>All shares of common stock that you purchase in the rights offering will be issued in book-entry, or uncertificated, form. All shares of Series C Preferred Stock will be certificated. When issued, the shares will be registered in the name of the subscription rights holder of record. As soon as practicable after the expiration of the rights offering, the subscription agent or the Company, as applicable, will arrange for the issuance of the shares of common stock or Series C Preferred Stock purchased in the rights offering. Subject to state securities laws and regulations, we have the discretion to delay distribution of any shares you may have elected to purchase by exercise of your subscription rights in order to comply with state securities laws.</p>
Certain Material U.S. Federal Tax Consequences to U.S. Holders	<p>For U.S. federal income tax purposes, we do not believe you should recognize income or loss in connection with the receipt or exercise of subscription rights in the rights offering. However the rules applicable to the receipt and exercise of subscription rights are complicated and unclear in certain respects, and it is possible that the Internal Revenue Service (“IRS”) could challenge our position. You are urged to consult your own tax advisor as to your particular tax consequences resulting from the receipt and exercise of subscription rights and the receipt, ownership and disposition of our common stock. For further information, please see “Material U.S. Federal Income Tax Consequences to U.S. Holders.”</p>
Subscription Agent	<p>Computershare Trust Company, N.A.</p>
Information Agent	<p>Alliance Advisors LLC</p>
Risk Factors	<p>Stockholders considering making an investment by exercising subscription rights in the rights offering should carefully read and consider the information set forth in “Risk Factors” beginning on page S-15 of this prospectus supplement, together with the other information contained in or incorporated by reference into this prospectus supplement and the accompanying prospectus, before making a decision to invest in our common stock.</p>
Nasdaq Global Select Market Symbol	<p>SPRO</p>

## RISK FACTORS

*An investment in our stock involves a high degree of risk. You should carefully read and consider the risks described below, together with the other information contained in or incorporated by reference into this prospectus supplement and the accompanying prospectus, including under the heading “Risk Factors” in our Annual Report on Form 10-K for the fiscal year ended December 31, 2018 and our Quarterly Reports on Form 10-Q for the quarterly periods ended subsequent to our filing of such Annual Report on Form 10-K before making a decision to invest in our common stock. The risks described below are not the only risks we face. Additional risks and uncertainties not currently known to us or that we currently deem to be immaterial may also materially and adversely affect our business operations. If any of the following risks actually occurs, our business, results of operations and financial condition could suffer. In that case, the trading price of our common stock could decline, and you may lose all or part of your investment.*

### Risks Related to the Rights Offering

***The price of our common stock is volatile and may decline after you exercise your subscription rights.***

The market price of our common stock is subject to wide fluctuations in response to numerous factors, including factors that have little or nothing to do with us or our performance, and these fluctuations could materially reduce our stock price. These factors include, among other things, the fact that our stock is relatively thinly traded, and as a result trades of small numbers of our shares can have a significant impact on the trading price of our stock, business conditions in our markets and the general state of the securities markets and the market for other biotechnology stocks, changes in capital markets that affect the perceived availability of capital to companies in our industry, governmental legislation or regulation and general economic and market conditions, such as recessions and downturns in the United States or global economy. In addition, the stock market historically has experienced significant price and volume fluctuations. These fluctuations are often unrelated to the operating performance of particular companies. These broad market fluctuations may cause declines in the market price of our common stock, which may make it difficult for you to resell shares of our common stock owned by you at times or at prices that you find attractive.

***If you do not fully exercise your subscription rights, your interest in us may be significantly diluted, and to the extent you do exercise your subscription rights and the subscription price is less than the fair value of our common stock, you would experience an immediate dilution of the aggregate fair value of your subscription shares, which could be substantial.***

Up to a maximum of 3,333,333 shares of common stock (or an equivalent number of shares of Series C Preferred Stock) are issuable in the rights offering and/or pursuant to the Backstop Commitment. Accordingly, if you do not exercise your subscription rights in full, your interest in us will be significantly diluted upon completion of the rights offering. In addition, if you do exercise your subscription rights and the subscription price is less than the fair value of our common stock, you would experience immediate dilution of the value of your subscription shares relative to what your value would have been had our common stock been issued at fair value. This dilution could be substantial.

***The subscription price determined for the rights offering is not an indication of the fair value of our common stock.***

Our Board of Directors considered a number of factors in determining the price for the rights offering, including:

- the price per share at which BVF is willing to backstop the rights offering;
- “pass through” savings as a result of conducting the rights offering with no investment banking support;

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- the price at which our stockholders might be willing to participate in the rights offering;
- historical and current trading prices for our common stock, including on a volume weighted average share price basis prior to the date on which BVF agreed to the backstop commitment; and
- the desire to provide an opportunity to our stockholders to participate in the rights offering on a pro rata basis.

The subscription price is not necessarily related to our book value, results of operations, cash flows, financial condition or net worth or any other established criteria of value and may or may not be considered the fair value of our common stock at the time the rights offering was approved by our Board of Directors or during the rights offering period. We cannot assure you that the trading price of our common stock will not decline after you exercise your subscription rights. We also cannot assure you that you will be able to sell shares purchased in this rights offering at a price equal to or greater than the subscription price. We do not intend to change the subscription price in response to changes in the trading price of our common stock prior to the closing of the rights offering.

***Our Board of Directors is not making any recommendations regarding your exercise of the subscription rights, and we did not receive a fairness opinion from a financial advisor in determining the subscription price or the terms of the rights offering.***

Our Board of Directors is not making any recommendations regarding your exercise of the subscription rights. In addition, we did not receive a fairness opinion from a financial advisor in determining the subscription price or the terms of the rights offering. Stockholders who exercise subscription rights risk investment loss on new money invested. We cannot assure you that the trading price for our common stock will be above the subscription price at the time of exercise or at the expiration of the rights offering period or that anyone purchasing shares at the subscription price will be able to sell those shares in the future at the same price or a higher price. You are urged to make your own decision whether or not to exercise your subscription rights based on your own assessment of our business and the rights offering.

***The rights offering may cause the price of our common stock to decline.***

The rights offering and its terms, including the subscription price, together with the number of shares of common stock we could issue if this rights offering is completed, may result in a decrease in the trading price of our common stock. This decrease may continue after the completion of the rights offering. If that occurs, your purchase of shares of our common stock in the rights offering may be at a price greater than the prevailing trading price. Further, if the holders of the shares received upon exercise of the subscription rights choose to sell some or all of their shares, the resulting sales could also depress the trading price of our common stock.

***Because you may not revoke or change your exercise of the subscription rights, you could be committed to buying shares above the prevailing trading price at the time the rights offering is completed.***

Once you exercise your subscription rights, you may not revoke or change the exercise. The trading price of our common stock may decline after you exercise your subscription right. If you exercise your subscription rights, and, afterwards, the trading price of our common stock decreases below the \$9.00 per share subscription price, you will have committed to buying shares of our common stock at a price above the prevailing trading price and could have an immediate unrealized loss. There can be no assurances that the trading price of our common stock will equal or exceed the subscription price at the time of exercise or at the expiration of the subscription rights offering period or thereafter.

***You may not be able to resell any shares of our common stock that you purchase pursuant to the exercise of subscription rights immediately upon expiration of the subscription rights offering period.***

If you exercise subscription rights, you may not be able to resell the common stock purchased by exercising your subscription rights until you, or your broker, custodian bank or other nominee, if applicable, have received those

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shares. Moreover, you will have no rights as a stockholder of the shares you purchased in the rights offering until we issue the shares to you. Although we will endeavor to issue the shares as soon as practicable after completion of the rights offering, including after all necessary calculations have been completed, there may be a delay between the expiration date of the rights offering and the time that the shares are issued.

***Because we will have broad discretion over the use of the net proceeds from the rights offering, you may not agree with how we use the proceeds.***

We are conducting the rights offering in order to raise additional capital and to improve and strengthen our financial position. We intend to use the net proceeds from the rights offering, together with our existing cash, cash equivalents and marketable securities and committed funding from our existing BARDA contract and other non-dilutive funding commitments, to fund the advancement of tebipenem HBr and the initiation of a Phase 2a clinical trial of SPR720 and the remainder for working capital and other general corporate purposes. However, we may allocate the proceeds among these purposes as we determine is appropriate. Moreover, economic, business and financial market conditions may require us to allocate portions of the net proceeds for other purposes. Accordingly, you will be relying on the judgment of our management with regard to the use of proceeds from the rights offering, and you will not have the opportunity, as part of your investment decision, to assess whether the proceeds are being used in a manner that you consider appropriate.

***Because the subscription rights are non-transferable, there is no market for the subscription rights.***

You may not sell, transfer or assign your subscription rights to anyone else. Because the subscription rights are non-transferable, there is no market or other means for you to directly realize any value associated with the subscription rights. You must exercise the subscription rights and acquire additional shares of our common stock to realize any value that may be embedded in the subscription rights.

### **Risks Related to Our Financial Position and Need for Additional Capital**

***We have a history of losses and expect to incur substantial future losses; because our funds currently on hand and the expected net proceeds from this offering will not be sufficient to fund our operations, as currently planned, for more than one year from the filing date of this prospectus supplement, we have determined that there is substantial doubt regarding our ability to continue as a going concern; we also expect that the report of our auditor on our consolidated financial statements for fiscal year 2019 will express substantial doubt about our ability to continue as a going concern.***

We are a clinical-stage biopharmaceutical company with a limited operating history. We have not generated any revenue from the sale of products and have incurred losses in each year since our inception in 2013. Our net loss was \$35.9 million for the nine months ended September 30, 2019. Our net loss was \$41.7 million for the year ended December 31, 2018. All of our product candidates are in development, none have been approved for sale and we may never have a product candidate approved for commercialization. We have financed our operations primarily through sales of our equity securities, collaborations and government funding for research and development.

Based on our current plans, we believe that our estimated cash, cash equivalents and marketable securities as of December 31, 2019, together with committed funding from our existing BARDA contract and other non-dilutive funding commitments, will not be sufficient to fund our operating expenses and capital expenditure requirements, as currently planned, for more than one year. Specifically we believe these funds will be sufficient to fund our operations into the fourth quarter of 2020, including through top-line data readout of our pivotal Phase 3 clinical trial of tebipenem HBr. Together with the expected proceeds of this offering, we believe these funds will be sufficient to fund our operations into the first quarter of 2021, including through the filing of an NDA for tebipenem HBr. We will require additional capital to fund the development of our product candidates through regulatory approval and commercialization.

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Because our funds currently on hand and the expected net proceeds from this offering will not be sufficient to fund our operations for more than one year beyond the filing date of this prospectus supplement, we have determined that there is substantial doubt regarding our ability to continue as a going concern. In connection with our future filing of our Annual Report on Form 10-K for the year ended December 31, 2019 (Form 10-K), we expect that we will disclose in such filing that we will not have sufficient liquidity to fund our operations for more than one year beyond the filing date of the Form 10-K and therefore that raises substantial doubt about our ability to continue as a going concern. As a result, we expect that the opinion from our independent registered public accounting firm on such annual financial statements will contain an explanatory paragraph about such substantial doubt about our ability to continue as a going concern.

The substantial doubt about our ability to continue as a going concern may adversely affect our stock price and our ability to raise capital. If we are unable to obtain additional capital, we may not be able to continue our operations on the scope or scale as currently conducted, and that could have a material adverse effect on our business, results of operations and financial condition.

## CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement and the accompanying prospectus, including the documents that we incorporate by reference herein and therein, contain “forward-looking statements” within the meaning of Section 27A of the Securities Act of 1933, as amended (the “Securities Act”), and Section 21E of the Securities Exchange Act of 1934, as amended (the “Exchange Act”). These forward-looking statements can generally be identified as such because the context of the statement will include words such as “may,” “will,” “intend,” “plan,” “believe,” “anticipate,” “expect,” “estimate,” “predict,” “potential,” “continue,” “likely,” or “opportunity,” the negative of these words or words of similar import. Similarly, statements that describe our future plans, strategies, intentions, expectations, objectives, goals or prospects are also forward-looking statements. Discussions containing these forward-looking statements may be found, among other places, in the “Business” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations” sections incorporated by reference from our most recent Annual Report on Form 10-K and our Quarterly Reports on Form 10-Q for the quarterly periods ended subsequent to our filing of such Annual Report on Form 10-K, as well as any amendments thereto reflected in subsequent filings with the SEC.

These forward-looking statements are based largely on our expectations and projections about future events and future trends affecting our business, and are subject to risks and uncertainties that could cause actual results to differ materially from those anticipated in the forward-looking statements. The risks and uncertainties include, among others, those noted in “Risk Factors” above and in any applicable prospectus supplement or free writing prospectus, and those included in the documents that we incorporate by reference herein and therein.

In addition, past financial and/or operating performance is not necessarily a reliable indicator of future performance, and you should not use our historical performance to anticipate results or future period trends. We can give no assurances that any of the events anticipated by the forward-looking statements will occur or, if any of them do, what impact they will have on our results of operations and financial condition. Except as required by law, we undertake no obligation to publicly revise our forward-looking statements to reflect events or circumstances that arise after the filing of this prospectus supplement or any applicable prospectus supplement or free writing prospectus, or documents incorporated by reference herein and therein, that include forward-looking statements.

## USE OF PROCEEDS

We estimate that we will receive net proceeds of approximately \$29.5 million from the sale of the shares of common stock and Series C Preferred Stock offered by us in the rights offering and/or pursuant to the Backstop Commitment, after deducting estimated offering expenses. We estimate that the expenses of the rights offering will be approximately \$0.5 million.

We intend to use the net proceeds from this offering, together with our existing cash, cash equivalents and marketable securities and committed funding from our existing BARDA contract and other non-dilutive funding commitments, to fund the advancement of tebipenem HBr and the initiation of a Phase 2a clinical trial of SPR720 and the remainder for working capital and other general corporate purposes. We believe opportunities may exist from time to time to expand our current business through acquisitions or in-licensing of complementary companies, medicines or technologies. While we have no current agreements, commitments or understandings for any specific acquisitions or in-licensing at this time, we may use a portion of the net proceeds for these purposes.

Together with the net proceeds of this offering, based on our current plans, we expect these funds to be sufficient to fund our operating expenses and capital expenditure requirements into the first quarter of 2021, including through the filing of an NDA for tebipenem HBr. 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 these funds to be sufficient to fund the development of our product candidates through regulatory approval and commercialization. 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.

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.

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.

## DILUTION

If you purchase shares of our common stock in this offering, you will experience dilution 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 rights offering. The net tangible book value of our common stock on September 30, 2019 was \$93.0 million, or \$4.98 per share (based upon 18,663,030 shares of our common stock outstanding). Net tangible book value per share is equal to the amount of our total tangible assets, less total liabilities, divided by the aggregate number of shares of our common stock outstanding.

After giving effect to the assumed sale in this rights offering by us of 3,333,333 shares of common stock (or an equivalent number of shares of Series C Preferred Stock) at a subscription price of \$9.00 per share and after deducting estimated offering expenses payable by us, our as-adjusted net tangible book value as of September 30, 2019 would have been \$122.5 million, or \$5.57 per share of common stock. This represents an immediate increase in net tangible book value of \$0.59 per share to existing stockholders and immediate dilution in net tangible book value of \$3.43 per share to investors purchasing shares of our common stock in this offering. The following table illustrates this per share dilution:

Subscription price per share of common stock	\$9.00
Net tangible book value per share as of September 30, 2019	\$4.98
Increase attributable to investors in this offering	<u>\$0.59</u>
As adjusted net tangible book value per share as of September 30, 2019 after giving effect to this offering	<u>\$5.57</u>
Dilution per share to investors participating in this offering	<u>\$3.43</u>

The discussion and table above do not take into account further dilution to investors in this offering that could occur upon the exercise of outstanding options and warrants having a per share exercise price less than the subscription price per share in this offering.

The number of shares of our outstanding common stock reflected in the discussion and table above is based on 18,663,030 shares of common stock outstanding as of September 30, 2019 and excludes:

- 1,720,000 shares of common stock issuable upon conversion of 1,720 shares of our Series A Preferred Stock as of September 30, 2019;
- 1,000,000 shares of common stock issuable upon conversion of 1,000 shares of our Series B Preferred Stock as of September 30, 2019;
- 3,094,930 shares of common stock issuable upon exercise of outstanding options as of September 30, 2019, having a weighted average exercise price of \$8.02 per share, of which 1,224,086 shares were vested as of such date;
- 50,000 shares of common stock issuable upon the vesting and release of outstanding restricted stock units as of September, 2019; and
- 371,443 shares of common stock reserved for future issuance as of September, 2019 under our 2017 Stock Incentive Plan, as amended, and our 2019 Inducement Equity Incentive Plan.

## DESCRIPTION OF THE RIGHTS OFFERING

Before deciding whether to exercise your subscription rights, you should carefully read this prospectus supplement and the accompanying prospectus, including the information set forth under the heading “Risk Factors” and the information that is incorporated by reference into this prospectus supplement and the accompanying prospectus, including our Annual Report on Form 10-K for the fiscal year ended December 31, 2018 and our Quarterly Reports on Form 10-Q for the quarterly periods ended subsequent to our filing of such Annual Report on Form 10-K.

### The Subscription Rights

We are distributing to the holders of record of our common stock, Series A Preferred Stock and Series B Preferred Stock (collectively, for purposes of the rights offering, “stockholders”) as of 5:00 p.m., New York time, on February 10, 2020, which is the record date for this rights offering, at no charge, non-transferable subscription rights to purchase shares of our common stock (subject to the aggregate offering threshold and certain ownership limitations). For each share of common stock (including shares of common stock issuable upon conversion of the Company’s outstanding shares of Series A Preferred Stock and Series B Preferred Stock) for which you are the holder of record as of 5:00 p.m., New York Time, on February 10, 2020, you will receive 0.152 rights to purchase shares of our common stock (subject to the aggregate offering threshold and certain ownership limitations). Each whole right will allow you to subscribe for one share of common stock at the subscription price (or an equivalent number of shares of Series C Preferred Stock) on the terms described in this prospectus supplement.

The total number of subscription rights issued to each holder will be rounded down to the nearest whole number.

You may exercise any number of your subscription rights, or you may choose not to exercise any subscription rights. The subscription rights will allocate the rights to purchase up to 3,333,333 shares of common stock (or an equivalent number of shares of Series C Preferred Stock) (the “offered pool”) *pro rata* among the stockholders entitled to participate as of the record date.

The subscription rights will be evidenced by subscription rights certificates. Subscription rights may be exercised at any time during the subscription period, which commences on February 11, 2020, through the expiration date for the rights offering, which is 5:00 p.m., New York time, on March 2, 2020. You are not required to exercise any of your subscription rights.

If any portion of the offered pool remains unpurchased at the end of the offering period, we will offer BVF the right to subscribe for up to the full amount of the unsubscribed portion of the offered pool (on the same terms and subject to the same conditions as set forth herein). BVF may elect to purchase unsubscribed shares in any combination of common stock and/or Series C Preferred Stock, as permitted by applicable Nasdaq rules. Separately, BVF has agreed to purchase a number of shares of Series C Preferred Stock with an aggregate value equal to the remaining unsubscribed portion of the securities offered by this prospectus supplement. See “Description of the Backstop Commitment.”

### Subscription Price

Our Board of Directors considered a number of factors in determining the price for the rights offering, including:

- the price per share at which BVF is willing to backstop the rights offering;
- “pass through” savings as a result of conducting the rights offering with no investment banking support;
- the price at which our stockholders might be willing to participate in the rights offering;
- historical and current trading prices for our common stock, including on a volume weighted average share price basis prior to the date on which BVF agreed to the backstop commitment; and

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- the desire to provide an opportunity to our stockholders to participate in the rights offering on *apro rata* basis.

See “Risk Factors—The subscription price determined for the rights offering is not an indication of the fair value of our common stock.”

### **Expiration Time and Date**

The subscription rights will expire at 5:00 p.m., New York time, on March 2, 2020, unless we extend the rights offering period. We reserve the right to extend the subscription period at our sole discretion. If the expiration date of the rights offering is so extended, we will give oral or written notice to the subscription agent on or before the scheduled expiration date, and we will issue a press release announcing such extension no later than 9:00 a.m., New York time, on the next business day after the most recently announced expiration of the rights offering. You must properly complete the subscription rights certificate distributed by the subscription agent and deliver it, along with the full subscription price, to the subscription agent prior to 5:00 p.m., New York time, on March 2, 2020, unless the expiration date is extended. After the expiration of the rights offering period, all unexercised subscription rights will be null and void. We will not be obligated to honor any purported exercise of subscription rights which the subscription agent receives after the expiration of the rights offering, regardless of when you sent the documents regarding that exercise. Shares purchased in the rights offering will be issued, and any subscription payments for shares not allocated or validly purchased will be returned, as soon as practicable following the expiration date of the rights offering.

### **Common Stock**

The material terms and provisions of our common stock and each other class of our securities which qualifies or limits our common stock are each described in the accompanying prospectus starting on page 10.

### **Series C Preferred Stock**

The material terms and provisions of the Series C Preferred Stock being offered pursuant to this prospectus supplement and the accompanying prospectus are summarized below. This summary is subject to, and qualified in its entirety by, the rights, preferences and privileges of the Series C Preferred Stock set forth in the certificate of amendment to our certificate of incorporation to be filed as an exhibit to our Current Report on Form 8-K that we expect to file with the SEC in connection with this rights offering.

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

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

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

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

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

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

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

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

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

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

### **Shares Outstanding After the Rights Offering**

As of the record date, there were 19,282,091 shares of our common stock outstanding, 1,720 shares of our Series A Preferred Stock outstanding, 1,000 shares of our Series B Preferred Stock outstanding, and no shares of our Series C Preferred Stock outstanding. We will issue up to a maximum of 3,333,333 shares of common stock

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(or an equivalent number of shares of Series C Preferred Stock) in the rights offering and/or pursuant to the Backstop Commitment. Based on the number of shares issued and outstanding as of the record date, if we issue all 3,333,333 shares of common stock available in this rights offering and/or pursuant to the Backstop Commitment, we would have 22,615,424 shares of common stock issued and outstanding following the completion of the rights offering, not including 2,720,000 shares of our common stock issuable upon the conversion of 2,720 shares of our Series A Preferred Stock and Series B Preferred Stock outstanding as of the record date.

The shares of our common stock are listed on the Nasdaq Global Select Market under the symbol “SPRO.”

### **Reasons for the Rights Offering**

We are conducting the rights offering in order to raise additional capital and to improve and strengthen our financial position. We intend to use the net proceeds from the rights offering to, together with our existing cash, cash equivalents and marketable securities and committed funding from our existing BARDA contract and other non-dilutive funding commitments, to fund the advancement of tebipenem HBr and the initiation of a Phase 2a clinical trial of SPR720 and the remainder for working capital and other general corporate purposes.

In authorizing the rights offering, our Board of Directors considered and evaluated a number of factors, including:

- our current capital resources and our future need for additional liquidity and capital;
- the size and timing of the rights offering;
- the potential dilution to our current stockholders if they choose not to participate in the rights offering;
- alternatives available for raising capital, including debt and other forms of equity raises;
- the potential impact of the rights offering on the public float for our common stock;
- BVF’s willingness to backstop the rights offering;
- that applicable Nasdaq marketplace rules do not require stockholder approval of the rights offering or the Backstop Commitment; and
- the fact that existing stockholders would have the opportunity to participate on a pro rata basis to purchase additional shares of common stock.

The net proceeds to us, after deducting estimated offering expenses, will be approximately \$29.5 million, assuming all shares of common stock or Series C Preferred Stock are issued in the rights offering and/or pursuant to the Backstop Commitment. We estimate that the expenses of the rights offering will be approximately \$0.5 million.

### **Investment Agreement**

We have entered into an Investment Agreement with BVF, pursuant to which BVF has agreed to provide the Backstop Commitment. For more information, see the section entitled “Description of the Backstop Commitment” of this prospectus supplement.

### **Limitations on the Purchase of Shares of Common Stock**

You may only purchase the number of whole shares of common stock purchasable upon exercise of the subscription rights distributed to you in the rights offering. Accordingly, the number of shares of common stock that you may purchase in the rights offering is limited by the number of our shares of common stock you held on the record date. We reserve the right to reject any or all subscriptions not properly submitted or the acceptance of which would, in the opinion of our counsel, be unlawful.

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In addition, we will not be required to issue to you shares of our common stock pursuant to the rights offering if, in our opinion, you are required to obtain prior clearance or approval from any state or federal regulatory authorities to own or control the shares and if, at the time the rights offering expires, you have not obtained this clearance or approval.

### **Method of Exercising Subscription Rights**

The exercise of subscription rights is irrevocable and may not be cancelled or modified. You may exercise your subscription rights as follows:

#### *Subscription by Registered Holders*

To exercise your subscription rights, you must properly complete and execute the subscription rights certificate, together with any required signature guarantees, and forward it, together with payment in full of the subscription price for each share of our common stock you are subscribing for, to the subscription agent at the address set forth under “Subscription Agent” below, on or prior to the expiration date.

#### *Subscription by Beneficial Owners*

If you are a beneficial owner of shares that holds your shares through a broker, custodian bank or other nominee, we will ask your broker, custodian bank or other nominee to notify you of the rights offering. If you wish to exercise your subscription rights, you will need to have your broker, custodian bank or other nominee act for you and exercise your subscription rights and deliver all documents and payment on your behalf prior to 5:00 p.m., New York time, on March 2, 2020. If you hold certificates of our common stock directly and would prefer to have your broker, custodian bank or other nominee act for you, you should contact your nominee and request it to effect the transactions for you.

To indicate your decision with respect to your subscription rights, you should complete and return to your broker, custodian bank or other nominee, the form entitled “Beneficial Owner Election Form.” You should receive this form from your broker, custodian bank or other nominee with the other subscription rights offering materials.

You should contact your broker, custodian bank or other nominee if you do not receive this form, but you believe you are entitled to participate in the rights offering. We are not responsible if you do not receive the form from your broker, custodian bank or nominee or if you receive it without sufficient time to respond.

#### *Medallion Guarantee May Be Required*

Your signature on the subscription rights certificate must be guaranteed by an eligible institution, such as a member firm of a registered national securities exchange or a member of the Financial Industry Regulatory Authority, or a commercial bank or trust company having an office or correspondent in the United States under certain circumstances provided for in the Instructions as to use of Rights Certificates and subject to standards and procedures adopted by the subscription agent, unless you are an eligible institution.

#### *Instructions for Completing Your Subscription Rights Certificate*

You should read the instruction letter accompanying the subscription rights certificate carefully and strictly follow it. Do not send subscription rights certificates or payments to us. We will not consider your subscription received until the subscription agent has received delivery of a properly completed and duly executed subscription rights certificate and payment of the full subscription amount. The risk of delivery of all documents and payments is borne by you or your nominee, not us or the subscription agent.

The method of delivery of subscription rights certificates and payment of the subscription amount to the subscription agent will be at the risk of the holders of subscription rights. If sent by mail, we recommend that you

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send those certificates and payments by overnight courier or by registered mail, properly insured, with return receipt requested, and that a sufficient number of days be allowed to ensure delivery to the subscription agent and clearance of payment before the expiration of the subscription period for the rights offering.

### *Validity of Subscriptions*

We will resolve all questions regarding the validity and form of the exercise of your subscription rights, including time of receipt and eligibility to participate in the rights offering. Our determination will be final and binding. Once made, subscriptions and directions are irrevocable, and we will not accept any alternative, conditional or contingent subscriptions or directions. We reserve the absolute right to reject any subscriptions or directions not properly submitted or the acceptance of which would be unlawful. You must resolve any irregularities in connection with your subscriptions before the subscription period expires, unless waived by us at our sole discretion. Neither the subscription agent nor we shall be under any duty to notify you or your representative of defects in your subscriptions. A subscription will be considered accepted, subject to our right to cancel the rights offering, only when a properly completed and duly executed subscription rights certificate and any other required documents and payment of the full subscription amount have been received by the subscription agent. Our interpretations of the terms and conditions of the rights offering will be final and binding.

### *No Revocation or Change*

Once you submit the form of subscription rights certificate to exercise any subscription rights, you are not allowed to revoke or change the exercise or request a refund of monies paid. All exercises of subscription rights are irrevocable. You should not exercise your subscription rights unless you are certain that you wish to purchase the shares of common stock offered pursuant to this rights offering.

## **Payment for Shares**

### *Method of Payment*

Your payment of the subscription price must be made in U.S. dollars for the full number of shares of common stock you wish to acquire in the rights offering by uncertified check payable to “Computershare Trust Company, N.A. (acting as subscription agent for Spero Therapeutics, Inc.)”

If you hold your rights through a broker, dealer, custodian bank or other nominee, you must deliver the applicable subscription payment and a completed form entitled “Beneficial Owner Election Form” (or such other appropriate documents as are provided by your nominee related to your subscription rights) to your nominee in each case, prior to the expiration of the rights offering.

### *Segregated Account; Return of Funds*

The subscription agent will hold funds received in payment for shares of the common stock in a segregated account pending completion of the rights offering. The subscription agent will hold this money until the rights offering is completed or is cancelled. If the rights offering is cancelled for any reason, the subscription agent will return this money to subscribers, without interest or penalty, as soon as practicable.

### *Receipt of Payment*

Your payment will be considered received by the subscription agent only upon clearance of any uncertified check deposited by the subscription agent.

Payment received after the expiration of the rights offering period will not be honored, and, in that case, the subscription agent will return your payment to you, without interest or penalty, as soon as practicable.

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### *Clearance of Uncertified Checks*

Please note that payment by uncertified personal check will not be deemed to have been received by the subscription agent until the check has cleared, which could take at least five or more business days to clear. We urge you to make payment sufficiently in advance of the time the rights offering expires to ensure that your payment is received by the subscription agent and clears by the rights offering expiration date.

### **Requirements for Foreign Stockholders**

Subscription rights certificates will only be mailed to stockholders whose addresses are within the United States (other than an APO or FPO address). Stockholders whose addresses are outside the United States or who have an APO or FPO address and who wish to subscribe to the rights offering either in part or in full should contact the subscription agent in writing or by recorded telephone conversation no later than five business days prior to the expiration date of the rights offering. The Company will determine whether the rights offering may be made to any such stockholder. The rights offering will not be made in any jurisdiction where it would be unlawful to do so. If the subscription agent has received no instruction by the fifth business day prior to the expiration date of the rights offering or the Company has determined that the rights offering may not be made to a particular stockholder, the rights will not be exercisable by such foreign stockholders, and any proceeds received by such foreign stockholders related to such rights will be refunded to such foreign stockholders, without interest.

### **Missing or Incomplete Subscription Information**

If you do not indicate the number of rights being exercised or complete the other required information, or do not forward full payment of the total subscription price payment for the number of subscription rights that you indicate are being exercised, then you will be deemed to have exercised your subscription rights with respect to the maximum number of subscription rights that may be exercised with the aggregate subscription price payment you delivered to the subscription agent. If we do not apply your full subscription price payment to your purchase of shares of our common stock, the subscription agent will return the excess amount to you by mail, without interest or penalty, as soon as practicable after the expiration date of the rights offering.

### **Amendment, Withdrawal and Termination**

The period for exercising your subscription rights may be extended by our Board of Directors in its reasonable discretion. Our Board of Directors does not currently intend to extend the expiration of the rights offering.

If we cancel the rights offering, in whole or in part, all affected subscription rights will expire without value, and all subscription payments received by the subscription agent will be returned, without interest or penalty, as soon as practicable. If we cancel the rights offering, we will issue a press release notifying stockholders of the cancellation.

### **Notice to Brokers and Nominees**

If you are a broker, custodian bank or other nominee holder that holds shares of our common stock for the account of others on the rights offering record date, you should notify the respective beneficial owners of such shares of the rights offering as soon as possible to learn their intentions with respect to exercising their subscription rights. You should obtain instructions from the beneficial owner with respect to their subscription rights, as set forth in the instructions we have provided to you for your distribution to beneficial owners. If the beneficial owner so instructs, you should complete the appropriate subscription rights certificates and submit them to the subscription agent with the proper payment. If you hold shares of our common stock for the account(s) of more than one beneficial owner, you may exercise the number of subscription rights to which all such beneficial owners in the aggregate otherwise would have been entitled had they been direct record holders of our common stock on the subscription rights offering record date, provided that you, as a nominee record holder, make a proper showing to the subscription agent by submitting the form entitled "Nominee Holder Certification" that we will provide to you with your subscription rights offering materials. If you did not receive this form, you should contact the subscription agent to request a copy.

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**Transferability of Subscription Rights**

The subscription rights granted to you are non-transferable and, therefore, you may not sell, transfer or assign your subscription rights to anyone else.

**Delivery of Shares**

All shares of common stock that you purchase in the rights offering will be issued in book-entry, or uncertificated, form. All shares of Series C Preferred Stock that you purchase in the rights offering will be certificated, provided that the underlying common stock (when and as issued on conversion) will be issued in book-entry form or delivered via DWAC to the converting stockholders' account (as requested by the stockholder). When issued, the shares will be registered in the name of the subscription rights holder of record.

As soon as practicable after the expiration of the rights offering, the subscription agent, in the case of the common stock, or the Company, in the case of the Series C Preferred Stock, will arrange for the issuance of the shares of common stock or Series C Preferred Stock purchased in the rights offering. Subject to state securities laws and regulations, we have the discretion to delay distribution of any shares you may have elected to purchase by exercise of your subscription rights in order to comply with state securities laws.

**Rights of Subscribers**

You will have no rights as a stockholder of our common stock until your account, or your account at your broker, custodian bank or other nominee is credited with the shares of our common stock purchased in the rights offering. You will have no right to revoke your subscriptions after you deliver your completed subscription rights certificate, payment and any other required documents to the subscription agent.

**No Recommendation to Subscription Rights Holders**

Our Board of Directors is making no recommendations regarding your exercise of the subscription rights. You are urged to make your own decision whether or not to exercise your subscription rights based on your own assessment of our business and the rights offering. See "Risk Factors" in this prospectus supplement and in any document incorporated by reference into this prospectus supplement and the accompanying prospectus.

**Miscellaneous**

*No Brokers, Dealers or Underwriters*

We have not employed any brokers, dealers or underwriters in connection with the solicitation of the exercise of subscription rights, and, except as described herein, no other commissions, underwriting fees or discounts will be paid in connection with this rights offering.

*Subscription Agent*

Computershare Trust Company, N.A. is acting as the subscription agent for the rights offering under an agreement with us. All subscription rights certificates, payments of the subscription price and nominee holder certifications, to the extent applicable to your exercise of subscription rights, must be delivered to Computershare Trust Company, N.A. as follows:

Computershare Trust Company, N.A.

By Mail:  
Computershare Trust Company, N.A.  
c/o Corporate Actions Voluntary Offer; COY: SPRO  
P.O. Box 43011  
Providence, RI 02940-3011

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By Overnight Courier:  
Computershare Trust Company, N.A.  
c/o Corporate Actions Voluntary Offer; COY: SPRO  
150 Royall Street, Suite V  
Canton, MA 02021

We will pay the fees and expenses of Computershare Trust Company, N.A. as subscription agent.

If you deliver subscription documents or subscription rights certificates in a manner different than that described in this prospectus supplement, then we may not honor the exercise of your subscription rights.

*Information Agent*

Alliance Advisors LLC is acting as the information agent for the rights offering under an agreement with us.

You should direct any questions or requests for assistance concerning the method of subscribing for the shares of common stock or Series C Preferred Stock or for additional copies of this prospectus supplement to Alliance Advisors LLC at 800-574-6215 or [reorg@allianceadvisorsllc.com](mailto:reorg@allianceadvisorsllc.com).

We will pay the fees and expenses of Alliance Advisors LLC, as information agent.

**Other Matters**

We are not making the rights offering in any state or other jurisdiction in which it is unlawful to do so, nor are we distributing or accepting any offers to purchase any shares of our common stock or Series C Preferred Stock from subscription rights holders who are residents of those states or other jurisdictions or who are otherwise prohibited by federal, state or foreign laws or regulations from accepting or exercising the subscription rights. We may delay the commencement of the rights offering in those states or other jurisdictions, or change the terms of the rights offering, in whole or in part, in order to comply with the securities laws or other legal requirements of those states or other jurisdictions. Subject to state securities laws and regulations, we also have the discretion to delay allocation and distribution of any shares you may elect to purchase in the rights offering in order to comply with state securities laws. We may decline to make modifications to the terms of the rights offering requested by those states or other jurisdictions, in which case, if you are a resident in those states or jurisdictions or if you are otherwise prohibited by federal, state or foreign laws or regulations from accepting or exercising the subscription rights, you will not be eligible to participate in the rights offering.

**Questions About Exercising Subscription Rights**

If you have any questions or require assistance regarding the method of exercising your subscription rights or requests for additional copies of this document or the Instructions as to the Use of Spero Therapeutics, Inc. Subscription Rights Certificates distributed by the subscription agent, you should contact the information agent, Alliance Advisors LLC, at 200 Broadacres Drive, 3rd Floor, Bloomfield, NJ 07003, 800-574-6215 or [reorg@allianceadvisorsllc.com](mailto:reorg@allianceadvisorsllc.com).

## DESCRIPTION OF THE BACKSTOP COMMITMENT

Below is a brief summary of matters related to the Backstop Commitment.

### Investment Agreement

On January 30, 2020, the Company entered into the Investment Agreement, pursuant to which BVF agreed to provide the Backstop Commitment, whereby BVF (and its assignee(s)/transferee(s)) has agreed to purchase from us, subject to certain conditions, shares of Series C Preferred Stock in an amount equal to the aggregate value of the shares of common stock not subscribed for in the rights offering, at a price per share equal to \$9,000 per share of Series C Preferred Stock (the “Backstop Commitment”). In addition to the investment under the Investment Agreement, as a stockholder as of the record date, BVF will have the right to subscribe for and purchase its pro rata share of our common stock and/or Series C Preferred Stock in the rights offering. If BVF does not exercise this purchase right in full, then it will be obligated to purchase an equivalent number of shares of our Series C Preferred Stock pursuant to the Backstop Commitment.

BVF’s obligation to provide the Backstop Commitment under the Investment Agreement is subject to certain conditions, including, but not limited to, the following: (i) the rights offering being completed in accordance with the terms and conditions of the Investment Agreement and this prospectus supplement; (ii) BVF having received certain notices from us; (iii) all governmental and third party notifications, filings, consents, waivers and approvals required for the consummation of the transactions contemplated by the Investment Agreement having been made or received; (iv) the accuracy of our representations and warranties made in the Investment Agreement; and (v) the absence of a material adverse effect, including (A) any outbreak of hostilities or escalation thereof or other calamity or crisis or any change or development involving a prospective change in national or international political, financial or economic conditions, (B) a suspension or material limitation on trading, or minimum or maximum prices for trading have been fixed, or maximum ranges for prices have been required, by Nasdaq Stock Market or any other securities exchange or by order of the SEC or any other governmental authority, (C) a material disruption in commercial banking or securities settlement or clearance services in the United States, or (D) a declaration of a banking moratorium by either Federal or New York authorities.

The Investment Agreement may be terminated by mutual written consent of the Company and BVF or by BVF if the Closing has not been consummated within ten (10) business days from the expiration of the offering period through no fault of BVF.

We are not paying a fee to BVF in connection with the Backstop Commitment. However, we have agreed to reimburse BVF for its reasonable legal fees and expenses in connection with the Investment Agreement and the rights offering, not to exceed \$50,000 in the aggregate.

### BVF Ownership

In connection with our July 2018 public offering, we issued 2,220 shares of our Series A Preferred Stock to certain affiliates of BVF, each share of which is convertible into 1,000 shares of our common stock, subject to certain ownership restrictions. In November 2018, we entered into an exchange agreement with BVF to exchange 1,000,000 shares of our common stock previously held by BVF for 1,000 shares of our Series B Preferred Stock, each share of which is convertible into 1,000 shares of our common stock, subject to certain ownership restrictions. In June 2019, BVF converted 500 shares of Series A Preferred Stock into 500,000 shares of our common stock pursuant to BVF’s rights under the certificate of designation for such Series A Preferred Stock.

As of the record date, BVF owned 495,405 shares of our common stock, representing approximately 2.6% of our outstanding common stock. If all of the Series A Preferred Stock and Series B Preferred Stock were converted,

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BVF would own 3,215,405 shares of our common stock, representing approximately 15% of our total outstanding common stock. As of the record date, 500 shares of the Series A Preferred Stock and none of the shares of Series B Preferred Stock issued to date have been converted into shares of our common stock.

Following completion of the rights offering and after giving effect to the Backstop Commitment, if no stockholders exercise their subscription rights in the rights offering, and BVF purchases all of its Backstop Commitment in shares of Series C Preferred Stock, BVF will own (a) 495,405 shares of our common stock, and (b) 1,720 shares of Series A Preferred Stock, 1,000 shares of Series B Preferred Stock, and 3,333 shares of Series C Preferred Stock, with such shares of Series A Preferred Stock, Series B Preferred Stock and Series C Preferred Stock representing an additional 6,053,000 shares of common stock on an as-converted basis (in each case subject to applicable conversion limits).

## **MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO U.S. HOLDERS**

The following discussion is a summary of the material U.S. federal income tax consequences to U.S. Holders (as defined below) relating to the receipt and exercise (or expiration) of the subscription rights acquired through the rights offering and the ownership and disposition of shares of our common stock and our Series C Preferred Stock received upon exercise of the subscription rights.

This summary deals only with subscription rights acquired through the rights offering and shares of our common stock or Series C Preferred Stock acquired upon exercise of subscription rights, in each case, that are held as capital assets by a beneficial owner. This discussion applies only to U.S. Holders and does not address all aspects of U.S. federal income taxation that may be relevant to U.S. Holders in light of their personal circumstances, including the alternative minimum tax and the Medicare contribution tax on investment income. This discussion also does not address tax consequences to U.S. Holders that may be subject to special tax rules, including, without limitation, insurance companies, real estate investment trusts, regulated investment companies, corporations that accumulate income to avoid U.S. federal income tax, grantor trusts, tax-exempt organizations, employee stock purchase plans, partnerships and other pass-through entities, persons holding subscription rights, shares of our common stock as part of a hedging, integrated, conversion or constructive sale transaction, a synthetic security or a straddle, or another risk reduction strategy, financial institutions, brokers, dealers in securities or currencies, traders that elect to mark-to-market their securities, persons that acquired subscription rights or shares of our common stock in connection with employment or other performance of services, and persons that have a functional currency other than the U.S. dollar. In addition, the discussion does not describe any tax consequences arising out of the tax laws of any state, local or foreign jurisdiction, or any U.S. federal tax considerations other than income taxation (such as estate, generation skipping or gift taxation).

The discussion below is based upon the provisions of the Internal Revenue Code of 1986, as amended, or the Code, the United States Treasury regulations promulgated thereunder, rulings and judicial decisions, as of the date hereof, and such authorities may be repealed, revoked or modified, perhaps retroactively. There can be no assurance that the IRS or a court (if the matter were contested) will not take positions concerning the tax consequences of the receipt of subscription rights acquired through the rights offering by persons holding shares of our common stock, Series A Preferred Stock or Series B Preferred Stock, the exercise (or expiration) of the subscription rights, or the acquisition, ownership and disposition of shares of our common stock and Series C Preferred Stock, in each case that are different from those discussed below.

As used herein, a “U.S. Holder” means a beneficial owner of shares of our common stock, subscription rights or shares of our common stock or Series C Preferred Stock acquired upon exercise of subscription rights, as the case may be, that is for U.S. federal income tax purposes: (1) an individual who is a citizen or resident of the United States; (2) a corporation (or other entity treated as a corporation for U.S. federal income tax purposes) created or organized in or under the laws of the United States or any state thereof or the District of Columbia; (3) an estate the income of which is subject to U.S. federal income taxation regardless of its source; or (4) a trust (a) the administration of which is subject to the primary supervision of a court within the United States and one or more United States persons as described in Section 7701(a)(30) of the Code have authority to control all substantial decisions of the trust or (b) that has a valid election under the Treasury Regulations in effect to be treated as a United States person.

If any entity or arrangement that is treated as a partnership or other pass-through entity for U.S. federal income tax purposes is the record owner, the U.S. federal income tax treatment of a partner (or participant in another pass-through entity) generally will depend upon the status of the person and the activities of the entity. Holders that are partnerships or other pass-through entities (and partners in such partnerships and participants in such entities) are urged to consult their own tax advisors.

**HOLDERS OF SHARES OF OUR COMMON STOCK, SERIES A PREFERRED STOCK AND SERIES B PREFERRED STOCK SHOULD CONSULT THEIR OWN TAX ADVISORS REGARDING THE**

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APPLICATION OF THE U.S. FEDERAL INCOME TAX LAWS TO THEIR PARTICULAR SITUATIONS AND THE CONSEQUENCES UNDER FEDERAL ESTATE AND GIFT TAX LAWS, FOREIGN, STATE AND LOCAL LAWS AND TAX TREATIES OF THE RECEIPT, OWNERSHIP AND EXERCISE OF SUBSCRIPTION RIGHTS AND THE ACQUISITION, OWNERSHIP AND DISPOSITION OF SHARES OF OUR COMMON STOCK OR SERIES C PREFERRED STOCK ACQUIRED UPON EXERCISE OF SUBSCRIPTION RIGHTS.

***Taxation of Subscription Rights***

*Receipt of Subscription Rights*

Although the authorities governing transactions such as this rights offering are complex and do not specifically address the consequences of certain aspects of this rights offering, including the effects of the oversubscription privilege, we do not believe your receipt of subscription rights pursuant to the rights offering should be treated as a taxable distribution with respect to your existing shares of common stock for U.S. federal income tax purposes. Pursuant to Section 305(a) of the Code, in general, the receipt by a stockholder of a right to acquire stock should not be included in the taxable income of the recipient. For purposes of Section 305(a), rights to acquire stock are treated as stock, so that holders of rights to acquire stock would be treated as stockholders. The general rule of non-recognition in Section 305(a) is subject to exceptions in Section 305(b), one of which relates to “disproportionate distributions.” A disproportionate distribution is a distribution or a series of distributions, including deemed distributions, that have the effect of the receipt of cash or other property by some stockholders and an increase in the proportionate interest of other stockholders in a corporation’s assets or earnings and profits. During the last 36 months, we have not made any distributions of cash or non-stock property with respect to our common stock. Currently we do not intend to make any future distributions of cash or non-stock property with respect to our common stock; however, there is no guarantee that we will not make such distributions in the future.

Our position regarding the tax-free treatment of the subscription rights distribution is not binding on the IRS or the courts. If our position is finally determined by the IRS or a court to be incorrect, whether on the basis that the issuance of the subscription rights is a “disproportionate distribution” or otherwise, the fair market value of the subscription rights would be taxable to holders of our common stock as a dividend to the extent of our current and accumulated earnings and profits, if any, with any excess being treated as a tax-free return of capital to the extent of the stockholder’s tax basis in our stock and then as capital gain. Although no assurance can be given, it is anticipated that we will not have current and accumulated earnings and profits through the end of 2020.

The following discussion is based upon the subscription rights issuance being treated as a non-taxable distribution with respect to your existing shares of common stock for U.S. federal income tax purposes.

*Tax Basis in the Subscription Rights*

If the fair market value of the subscription rights you receive in respect of your existing shares of common stock is less than 15% of the fair market value of your existing shares of common stock on the date you receive the subscription rights, the subscription rights will have a zero dollar basis for U.S. federal income tax purposes, unless you elect to allocate your basis in your existing shares of common stock between those existing holdings and the subscription rights in proportion to the relative fair market values of the existing holdings and the subscription rights, each determined on the date of receipt of the subscription rights. If you elect to allocate basis between your existing holdings and the subscription rights, you must make this election on a statement included with a timely filed tax return (including extensions) for the taxable year in which you receive the subscription rights. The election is irrevocable.

If the fair market value of the subscription rights you receive in respect of your existing shares common stock is 15% or more of the fair market value of your existing shares of common stock on the date you receive the subscription rights, then you must allocate the basis in your existing holdings between those holdings and the subscription rights in proportion to their fair market values determined on the date you receive the subscription rights.

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The fair market value of the subscription rights on the date that the subscription rights are distributed is uncertain, and we have not obtained, and do not intend to obtain, an appraisal of the fair market value of the subscription rights on that date. In determining the fair market value of the subscription rights, you should consider all relevant facts and circumstances, including but not limited to any difference between the subscription price of the subscription rights and the trading price of our shares of common stock on the date that the subscription rights are distributed, the length of the period during which the subscription rights may be exercised and the fact that the subscription rights are non-transferable.

### *Exercise of Subscription Rights*

Generally, you will not recognize gain or loss upon the exercise of a subscription right received pursuant to the rights offering. Your adjusted tax basis in the shares of common stock or Series C Preferred Stock acquired through the exercise of such subscription rights should equal the sum of (i) the subscription price paid for the shares, plus (ii) your tax basis, if any, in the subscription rights immediately prior to such exercise. The holding period for shares of common stock or Series C Preferred Stock acquired upon exercise of such subscription rights will begin on the date the subscription right is exercised.

If you exercise a subscription right received in the rights offering after disposing of the shares of our common stock, Series A Preferred Stock or Series B Preferred Stock with respect to which such subscription right is received, then certain aspects of the tax treatment of the exercise of the subscription right are unclear, including (1) the allocation of the tax basis between the shares of common stock or preferred stock previously sold and the subscription right, (2) the impact of such allocation on the amount and timing of gain or loss recognized with respect to the shares of our common stock or preferred stock previously sold and (3) the impact of such allocation on the tax basis of the shares of our common stock or Series C Preferred Stock acquired upon exercise of the subscription right. If you exercise a subscription right received in the rights offering after disposing of shares of common stock or preferred stock with respect to which such subscription right is received, you should consult with your own tax advisor.

### *Expiration of Subscription Rights*

If you allow subscription rights received in the rights offering to expire, you should not recognize any gain or loss for U.S. federal income tax purposes, and you should re-allocate any portion of the tax basis in your existing shares of common stock or previously allocated to the expired subscription rights to the existing shares of common stock.

## ***Taxation of Common Stock and Series C Preferred Stock***

### *Distributions*

Distributions with respect to shares of our common stock or Series C Preferred Stock acquired upon exercise of subscription rights will be taxable as dividend income when the distribution is actually or constructively received to the extent of our current or accumulated earnings and profits as determined for U.S. federal income tax purposes.

Dividend income received by certain non-corporate U.S. Holders with respect to shares of our common stock or Series C Preferred Stock generally will be "qualified dividends" subject to preferential rates of U.S. federal income tax, provided that the U.S. Holder meets applicable holding period and other requirements. Subject to similar exceptions for short-term and hedged positions, dividend income on our shares of common stock and Series C Preferred Stock paid to U.S. Holders that are domestic corporations generally will qualify for the dividends-received deduction. To the extent that the amount of a distribution exceeds our current and accumulated earnings and profits, the distribution will be treated first as a tax-free return of capital to the extent of your adjusted tax basis in your shares of our common stock or Series C Preferred Stock and thereafter as capital gain.

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*Dispositions*

If you sell or otherwise dispose of shares of common stock or Series C Preferred Stock acquired upon exercise of subscription rights in a taxable transaction, you will generally recognize capital gain or loss equal to the difference between the amount realized and your adjusted tax basis in the shares. The capital gain or loss will be long-term capital gain or loss if your holding period for the shares is more than one year at the time of disposition. Long-term capital gain of a non-corporate U.S. Holder is generally taxed at preferential rates of U.S. federal income tax. The deductibility of capital losses is subject to limitations.

***Information Reporting and Backup Withholding***

You may be subject to information reporting and/or backup withholding if you receive dividend payments (including constructive dividends) or receive gross proceeds from the disposition of shares of our common stock or Series C Preferred Stock acquired through the exercise of subscription rights. Backup withholding (currently at the rate of 24%) may apply under certain circumstances if you (1) fail to furnish your social security or other taxpayer identification number, or TIN, (2) furnish an incorrect TIN, (3) fail to report interest or dividends properly or (4) fail to provide a certified statement, signed under penalty of perjury, that the TIN provided is correct, that you are not subject to backup withholding and that you are a U.S. person for U.S. federal income tax purposes on IRS Form W-9. Any amount withheld from a payment under the backup withholding rules is allowable as a credit against (and may entitle you to a refund with respect to) your U.S. federal income tax liability, provided that the required information is timely furnished to the IRS. Certain persons, including corporations and certain financial institutions, that demonstrate this fact, if requested, are exempt from information reporting and backup withholding. You are urged to consult your own tax advisor as to your qualification for exemption from backup withholding and the procedure for obtaining such exemption.

THE PRECEDING DISCUSSION OF MATERIAL U.S. FEDERAL INCOME TAX CONSEQUENCES TO U.S. HOLDERS IS NOT TAX ADVICE. HOLDERS OF SUBSCRIPTION RIGHTS AND SHARES OF OUR COMMON STOCK, SERIES A PREFERRED STOCK AND SERIES B PREFERRED STOCK SHOULD CONSULT THEIR OWN TAX ADVISORS REGARDING THE APPLICATION OF THE U.S. FEDERAL INCOME TAX LAWS TO THEIR PARTICULAR SITUATIONS AND THE CONSEQUENCES UNDER FEDERAL ESTATE AND GIFT TAX LAWS, FOREIGN, STATE AND LOCAL LAWS AND TAX TREATIES OF THE RECEIPT, OWNERSHIP AND EXERCISE OF SUBSCRIPTION RIGHTS AND THE ACQUISITION, OWNERSHIP AND DISPOSITION OF SHARES OF OUR COMMON STOCK OR SERIES C PREFERRED STOCK ACQUIRED UPON EXERCISE OF SUBSCRIPTION RIGHTS.

## PLAN OF DISTRIBUTION

We will distribute the subscription rights, subscription rights certificates and copies of this prospectus supplement and the accompanying prospectus to holders of our common stock, Series A Preferred Stock or Series B Preferred Stock as of 5:00 p.m., New York time, on February 10, 2020, the record date for the rights offering. If you wish to exercise your subscription rights and purchase shares of common stock or Series C Preferred Stock (as applicable), you should complete the subscription rights certificate and return it with payment for the shares, to the subscription agent, Computershare Trust Company, N.A. See “Description of the Rights Offering—Method of Exercising Subscription Rights.” If you have any questions, you should contact the information agent, Alliance Advisors LLC, at 200 Broadacres Drive, 3rd Floor, Bloomfield, NJ 07003, 800-574-6215 or reorg@allianceadvisorsllc.com. The subscription rights will not be listed on any stock exchange or market or on the OTC Markets. Our shares of common stock are listed on The Nasdaq Global Select Market under the symbol “SPRO.”

We have agreed to pay the subscription agent and information agent customary fees plus certain expenses in connection with the rights offering. We have not employed any brokers, dealers or underwriters in connection with the solicitation of exercise of subscription rights. Except as described in this section, we are not paying any other commissions, underwriting fees or discounts in connection with the rights offering. Some of our employees may solicit responses from you as a holder of subscription rights, but we will not pay our employees any commissions or compensation for these services other than their normal employment compensation. We estimate that our total expenses in connection with the rights offering will be approximately \$0.5 million.

## **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 hereby.

## **EXPERTS**

The financial statements incorporated in this prospectus supplement by reference to the Annual Report on Form 10-K for the year ended December 31, 2018 have been so incorporated in reliance on the report (which contains an explanatory paragraph relating to the Company's requirement for additional financing to fund future operations as described in Note 1 to the consolidated financial statements) of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

## **WHERE YOU CAN FIND MORE INFORMATION**

We are subject to the reporting requirements of the Exchange Act and file annual, quarterly and current reports, proxy statements and other information with the SEC. SEC filings are available at the SEC's web site at <http://www.sec.gov>. This prospectus is only part of a registration statement on Form S-3 that we have filed with the SEC under the Securities Act and therefore omits certain information contained in the registration statement. We have also filed exhibits and schedules with the registration statement that are excluded from this prospectus, and you should refer to the applicable exhibit or schedule for a complete description of any statement referring to any contract or other document.

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

## INCORPORATION BY REFERENCE

This prospectus supplement and the accompanying prospectus is part of a registration statement on Form S-3. The SEC allows this filing to “incorporate by reference” information that we previously have filed with the SEC. This means we can disclose important information to you by referring you to other documents that we have filed with the SEC. The information that is incorporated by reference is considered part of this prospectus supplement and the accompanying prospectus, and information that we file later will automatically update and may supersede this information. For further information about our company and the securities being offered, you should refer to the registration statement and the following documents that are incorporated by reference:

- our Annual Report on [Form 10-K](#) for the fiscal year ended December 31, 2018 filed with the SEC on March 14, 2019;
- our Quarterly Reports on Form 10-Q for the fiscal quarters ended [March 31, 2019](#), [June 30, 2019](#) and [September 30, 2019](#) filed with the SEC on May 9, 2019, August 8, 2019 and November 4, 2019, respectively;
- our Current Reports on Form 8-K filed with the SEC on [January 7, 2019](#), [March 19, 2019](#), [March 29, 2019](#), [April 18, 2019](#), [June 6, 2019](#), [June 13, 2019](#), [September 6, 2019](#), [December 19, 2019](#), [January 30, 2020](#) and [February 11, 2020](#);
- the portions of our definitive Proxy Statement on Schedule 14A filed with the SEC on April 26, 2019 that are incorporated by reference into our Annual Report on Form 10-K for the fiscal year ended December 31, 2018; and
- the description of our common stock contained in our Registration Statement on [Form 8-A](#) initially filed with the SEC on October 30, 2017, including any amendment or report filed for the purpose of updating such description.

In addition, all documents filed by us under Sections 13(a), 14 or 15(d) of the Exchange Act (excluding, unless otherwise provided in this prospectus supplement or in the applicable document, documents not deemed “filed” with the SEC and information furnished pursuant to Item 2.02 and Item 7.01 on any Current Report on Form 8-K or certain exhibits furnished pursuant to Item 9.01 of Form 8-K), after the date of this prospectus supplement but before the termination of the rights offering covered by this prospectus supplement, are hereby incorporated by reference herein. We have not authorized anyone to provide you with any different or additional information other than that contained in or incorporated by reference into this prospectus supplement and the accompanying prospectus. We take no responsibility for, and can provide no assurance as to the reliability of, any information that others may provide.

Any statement contained in a document incorporated or deemed to be incorporated by reference into this prospectus supplement or the accompanying prospectus will be deemed to be modified or superseded for purposes of this prospectus supplement to the extent that a statement contained in this prospectus supplement or any other subsequently filed document that is deemed to be incorporated by reference into this prospectus supplement 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 supplement.

The documents incorporated by reference into this prospectus supplement and the accompanying prospectus are available from us upon request. We will provide a copy of any and all of the documents incorporated by reference (excluding exhibits, unless the exhibits are specifically incorporated), without charge, upon written or oral request. Requests for any of these documents should be directed to:

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

PROSPECTUS

# Spero Therapeutics, Inc.

**\$200,000,000**

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

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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.

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**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.**

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**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](http://www.sperotherapeutics.com). The information contained on, or that can be accessed through, our website is not part of this prospectus. Investors should not rely on any such information in deciding whether to purchase our securities.

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

***Offerings Under This Prospectus***

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

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

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

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

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

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

## **RISK FACTORS**

Investing in our securities involves significant risk. The prospectus supplement applicable to each offering of our securities will contain a discussion of the risks applicable to an investment in Spero. Prior to making a decision about investing in our securities, you should carefully consider the specific factors discussed under the heading “Risk Factors” in the applicable prospectus supplement, together with all of the other information contained or incorporated by reference in the prospectus supplement or appearing or incorporated by reference in this prospectus. You should also consider the risks, uncertainties and assumptions discussed under the heading “Risk Factors” included in our most recent Annual Report on Form 10-K, as revised or supplemented by our subsequent Quarterly Reports on Form 10-Q or our Current Reports on Form 8-K that we have filed with the SEC, all of which are incorporated herein by reference, and which may be amended, supplemented or superseded from time to time by other reports we file with the SEC in the future. The risks and uncertainties we have described are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also affect our operations. The occurrence of any of these risks might cause you to lose all or part of your investment in the offered securities.

## SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the documents incorporated by reference in this prospectus include forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, that relate to future events or our future financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to differ materially from any future results, levels of activity, performance or achievements expressed or implied by these forward-looking statements. Words such as, but not limited to, “believe,” “expect,” “anticipate,” “estimate,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “targets,” “likely,” “will,” “would,” “could,” “should,” “continue,” and similar expressions or phrases, or the negative of those expressions or phrases, are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Although we believe that we have a reasonable basis for each forward-looking statement contained in this prospectus and incorporated by reference in this prospectus, we caution you that these statements are based on our projections of the future that are subject to known and unknown risks and uncertainties and other factors that may cause our actual results, level of activity, performance or achievements expressed or implied by these forward-looking statements, to differ. The sections in our periodic reports, including our most recent Annual Report on Form 10-K, as revised or supplemented by our subsequent Quarterly Reports on Form 10-Q or our Current Reports on Form 8-K, entitled “Business,” “Risk Factors,” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations,” as well as other sections in this prospectus and the other documents or reports incorporated by reference in this prospectus, discuss some of the factors that could contribute to these differences. These forward-looking statements include, among other things, statements about:

- our use of the net proceeds from this offering;
- the initiation, timing, progress and results of, including interim data from, our preclinical studies and clinical trials, and our research and development programs;
- our ability to retain the continued service of our key professionals and to identify, hire and retain additional qualified professionals;
- our ability to advance product candidates into, and successfully complete, clinical trials;
- the timing or likelihood of regulatory filings and approvals;
- the commercialization of our product candidates, if approved;
- the pricing, coverage and reimbursement of our product candidates, if approved;
- the implementation of our business model, strategic plans for our business and product candidates and our Potentiator Platform;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates and our Potentiator Platform;
- our ability to enter into strategic arrangements and/or collaborations and the potential benefits of such arrangements;
- our estimates regarding expenses, capital requirements and needs for additional financing;
- our financial performance; and
- developments relating to our competitors and our industry.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important cautionary statements in this prospectus and in the documents

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incorporated by reference in this prospectus, particularly in the “Risk Factors” section, that we believe could cause actual results or events to differ materially from the forward-looking statements that we make. For a summary of such factors, please refer to the section entitled “Risk Factors” in this prospectus, as updated and supplemented by the discussion of risks and uncertainties under “Risk Factors” contained in any supplements to this prospectus and in our most recent Annual Report on Form 10-K, as revised or supplemented by our subsequent Quarterly Reports on Form 10-Q or our Current Reports on Form 8-K, as well as any amendments thereto, as filed with the SEC and which are incorporated herein by reference. The information contained in this document is believed to be current as of the date of this document. We do not intend to update any of the forward-looking statements after the date of this document to conform these statements to actual results or to changes in our expectations, except as required by law.

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

## **USE OF PROCEEDS**

Unless otherwise indicated in the applicable prospectus supplement, we intend to use any net proceeds from the sale of securities under this prospectus for general corporate purposes, including, but not limited to, clinical trials, research and development activities, working capital, capital expenditures, investments, acquisitions, should we choose to pursue any, and collaborations. We have not determined the amounts we plan to spend on any of the areas listed above or the timing of these expenditures. As a result, our management will have broad discretion to allocate the net proceeds, if any, we receive in connection with securities offered pursuant to this prospectus for any purpose. Pending application of the net proceeds as described above, we may initially invest the net proceeds in short-term, investment-grade, interest-bearing securities or apply them to the reduction of short-term indebtedness.

## PLAN OF DISTRIBUTION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## DESCRIPTION OF COMMON STOCK

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

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

### *General*

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

### *Transfer Agent and Registrar*

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

### *Stock Exchange Listing*

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

## DESCRIPTION OF PREFERRED STOCK

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

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

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

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

### *Series A Preferred Stock*

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

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

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

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

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

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

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

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

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

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

### ***Series B Preferred Stock***

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

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

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

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

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

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

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*pari passu* with the holders of common stock (on an as-converted basis, without regard to the 9.99% beneficial ownership limitation) and any securities having (by their terms) parity with the Series B Preferred Stock, including the Series A Preferred Stock, in the remaining distribution of the net assets of the Company available for distribution.

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

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

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

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

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

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

## DESCRIPTION OF DEBT SECURITIES

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

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

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

### *General*

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

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

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

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

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

### ***Conversion or Exchange Rights***

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

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

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

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

### ***Events of Default Under the Indenture***

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

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

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

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

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

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

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

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

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

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

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

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

### ***Modification of Indenture; Waiver***

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

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

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

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

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

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***Discharge***

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

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

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

***Form, Exchange and Transfer***

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

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***Information Concerning the Debenture Trustee***

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

***Payment and Paying Agents***

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

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

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

***Governing Law***

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

***Subordination of Subordinated Debt Securities***

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

## DESCRIPTION OF WARRANTS

### *General*

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

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

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

### *Transfer Agent and Registrar*

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

## DESCRIPTION OF RIGHTS

### *General*

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

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

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

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

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

***Rights Agent***

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

## DESCRIPTION OF UNITS

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

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

### *General*

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

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

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

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

### *Unit Agent*

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

### *Issuance in Series*

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

### *Enforceability of Rights by Holders of Units*

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

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

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

**Anti-Takeover Provisions**

***Delaware Law***

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

***Charter Documents***

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

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

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

Our amended and restated bylaws establish advance notice procedures with regard to stockholder proposals relating to the nomination of candidates for election as directors or new business to be brought before meetings of our stockholders. These procedures provide that notice of stockholder proposals must be timely given in

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writing to our corporate secretary prior to the meeting at which the action is to be taken. Generally, to be timely, notice must be received at our principal executive offices not less than 90 days or more than 120 days prior to the first anniversary date of the annual meeting for the preceding year. The notice must contain certain information specified in our amended and restated bylaws. These provisions may have the effect of precluding the conduct of certain business at a meeting if the proper procedures are not followed. These provisions may also discourage or deter a potential acquirer from conducting a solicitation of proxies to elect the acquirer's own slate of directors or otherwise attempting to obtain control of our company.

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

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

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

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

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

Our amended and restated certificate of incorporation provides that we will indemnify each person who was or is a party or threatened to be made a party to any threatened, pending or completed action, suit or proceeding whether civil, criminal, administrative or investigative (other than an action by or in the right of us) by reason of the fact that he or she is or was, or has agreed to become, our director or officer, or is or was serving, or has agreed to serve, at our request as a director, officer, partner, employee or trustee of, or in a similar capacity with, another corporation, partnership, joint venture, trust or other enterprise (all such persons being referred to as an "Indemnitee"), or by reason of any action alleged to have been taken or omitted in such capacity, against all expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred in connection with such action, suit or proceeding and any appeal therefrom, if such Indemnitee acted in good faith and in a manner he or she reasonably believed to be in, or not opposed to, our best interests, and, with respect to any criminal action or proceeding, he or she had no reasonable cause to believe his or her conduct was unlawful. Our amended and restated certificate of incorporation also provides that we will advance expenses to Indemnitees in connection with a legal proceeding, subject to limited exceptions.

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

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

**LEGAL MATTERS**

Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., Boston, Massachusetts, will pass upon the validity of the issuance of the securities to be offered by this prospectus.

**EXPERTS**

The financial statements incorporated in this prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2017 have been so incorporated in reliance on the report (which contains an explanatory paragraph relating to the Company's requirement for additional financing to fund future operations as described in Note 1 to the consolidated financial statements) of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in accounting and auditing.

### WHERE YOU CAN FIND MORE INFORMATION

We are subject to the reporting requirements of the Exchange Act and file annual, quarterly and current reports, proxy statements and other information with the SEC. SEC filings are available at the SEC's web site at <http://www.sec.gov>. This prospectus is only part of a registration statement on Form S-3 that we have filed with the SEC under the Securities Act and therefore omits certain information contained in the registration statement. We have also filed exhibits and schedules with the registration statement that are excluded from this prospectus, and you should refer to the applicable exhibit or schedule for a complete description of any statement referring to any contract or other document.

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

## INCORPORATION OF DOCUMENTS BY REFERENCE

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

- our Annual Report on [Form 10-K](#) for the fiscal year ended December 31, 2017, filed with the SEC on April 2, 2018;
- the information incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2017 from our definitive [Proxy Statement](#) for our 2018 Annual Meeting of Stockholders, filed with the SEC on April 27, 2018;
- our Quarterly Reports on Form 10-Q for the fiscal quarters ended March 31, 2018, June 30, 2018 and September 30, 2018, filed with the SEC on [May 10, 2018](#), [August 9, 2018](#) and [November 8, 2018](#), respectively;
- our Current Reports on Form 8-K, filed with the SEC on [January 23, 2018](#), [February 1, 2018](#), [June 8, 2018](#), [July 9, 2018](#), [July 16, 2018](#), [July 17, 2018](#), [August 14, 2018](#), [November 13, 2018](#) and [November 16, 2018](#) (except for the information furnished under Items 2.02 or 7.01 and the exhibits furnished thereto);
- the description of our common stock contained in our Registration Statement on [Form 8-A](#) initially filed on October 30, 2017, including any amendment or report filed for the purpose of updating such description; and
- all reports and other documents subsequently filed by us pursuant to Sections 13(a), 13(c), 14 and 15(d) of the Exchange Act after the date of this prospectus and prior to the termination or completion of the offering of securities under this prospectus shall be deemed to be incorporated by reference in this prospectus and to be a part hereof from the date of filing such reports and other documents.

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

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

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

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

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

You may also access these documents on our website, <http://www.sperotherapeutics.com>. The information contained on, or that can be accessed through, our website is not a part of this prospectus. We have included our website address in this prospectus solely as an inactive textual reference.

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



**Up to 3,333,333 Shares of Common Stock**  
**Up to 3,333 Shares of Series C Convertible Preferred Stock**

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**Prospectus Supplement**

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**February 11, 2020**

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