

---

---

**UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION**  
Washington, D.C. 20549

---

**FORM 8-K**

---

**CURRENT REPORT  
Pursuant to Section 13 OR 15(d)  
of the Securities Exchange Act of 1934**

**Date of Report (Date of earliest event reported) February 11, 2020**

---

**SPERO THERAPEUTICS, INC.**  
(Exact name of registrant as specified in its charter)

---

**Delaware**  
(State or other jurisdiction  
of incorporation)

**001-38266**  
(Commission  
File Number)

**46-4590683**  
(IRS Employer  
Identification No.)

**675 Massachusetts Avenue, 14th Floor**  
**Cambridge, Massachusetts**  
(Address of principal executive offices)

**02139**  
(Zip Code)

**Registrant's telephone number, including area code (857)242-1600**

---

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, \$0.001 par value per share	SPRO	The Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

---

---

---

**Item 2.02. Results of Operations and Financial Condition.**

The information provided in Item 8.01 of this Current Report on Form 8-K under the caption “*Recent Developments – Preliminary Estimate of Cash Balance as of December 31, 2019, Updated Cash Runway Statement and Our Ability to Continue as a Going Concern*” regarding the estimated cash, cash equivalents and marketable securities as of December 31, 2019 of Spero Therapeutics, Inc. (the “Company”) is incorporated by reference into this Item 2.02.

**Item 8.01. Other Events.**

On February 11, 2020, the Company issued a press release announcing the commencement of a rights offering to stockholders (the “Rights Offering”). A copy of the press release is filed as Exhibit 99.8 hereto. In connection with the Rights Offering, the Company is filing items included as Exhibits 99.1 through 99.7 to this Current Report on Form 8-K for the purpose of incorporating such items as exhibits to the Company’s Registration Statement on Form S-3 (Registration No. 333-228661), of which the prospectus supplement dated February 11, 2020 relating to the Rights Offering is a part (the “Prospectus Supplement”).

The “*Recent Developments*” section set forth in the “*Prospectus Supplement Summary*” section of the Prospectus Supplement referred to above is reproduced below:

**“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 (Form10-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 Form10-K for the year ended December 31, 2019.”

---

**Item 9.01. Financial Statements and Exhibits.**

(d) Exhibits.

<u>Number</u>	<u>Exhibit Description</u>
99.1	<a href="#">Form of Instructions as to use of Subscription Rights Certificates</a>
99.2	<a href="#">Form of Letter to Stockholders who are Record Holders</a>
99.3	<a href="#">Form of Letter to Stockholders who are Beneficial Holders</a>
99.4	<a href="#">Form of Letter to Clients of Stockholders who are Beneficial Holders</a>
99.5	<a href="#">Beneficial Owner Election</a>
99.6	<a href="#">Form of Nominee Holder Certification</a>
99.7	<a href="#">Form of Subscription Rights Certificate</a>
99.8	<a href="#">Press release dated February 11, 2020</a>

**Forward-Looking Statement**

*Investors are cautioned that statements in this Current Report on Form 8-K regarding the intention, completion and timing relating to the Rights Offering, the intended use of proceeds from the Rights Offering and the Company's future development plans for its product candidates and the timing and costs thereof constitute forward-looking statements that involve risks and uncertainties, including, without limitation, risks and uncertainties related to market conditions and the satisfaction of customary closing conditions related to the Rights Offering and the uncertainties inherent in the research and clinical development process. Additional information on risks facing the Company can be found under the heading "Risk Factors" in the Company's periodic reports, including its annual report on Form 10-K and quarterly reports on Form 10-Q, and in the Prospectus Supplement relating to the Rights Offering filed with the SEC, each available on the SEC's web site at [www.sec.gov](http://www.sec.gov). The Company expressly disclaims any obligation or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein to reflect any change in its expectations with regard thereto or any change in events, conditions or circumstances on which any such statements are based.*

---

**SIGNATURES**

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: February 11, 2020

SPERO THERAPEUTICS, INC.

/s/ Stephen DiPalma

Stephen DiPalma

Interim Chief Financial Officer and Treasurer

**FORM OF INSTRUCTIONS AS TO USE OF  
SPERO THERAPEUTICS, INC.  
SUBSCRIPTION RIGHTS CERTIFICATES**

**CONSULT THE INFORMATION AGENT, YOUR BANK OR YOUR BROKER AS TO ANY QUESTIONS**

The following instructions relate to a rights offering (the "Rights Offering") by Spero Therapeutics, Inc., a Delaware corporation (the "Company"), to the holders of record (the "Recordholders") of the Company's common stock, par value \$0.001 per share (the "Common Stock"), Series A convertible preferred stock, par value \$0.001 per share (the "Series A Preferred Stock"), and Series B convertible preferred stock, par value \$0.001 per share (the "Series B Preferred Stock"), as described in the prospectus supplement (and the accompanying prospectus) dated February 11, 2020 (the "Prospectus").

In the Rights Offering, Recordholders as of 5:00 p.m., New York time, on February 10, 2020 (the "Record Date"), are receiving, at no charge, non-transferable subscription rights (the "Rights") to subscribe for and purchase up to an aggregate of 3,333,333 shares of Common Stock and up to an aggregate of 3,333 shares of non-voting Series C convertible preferred stock, par value \$0.001 per share (the "Series C Preferred Stock") (collectively, the "Rights Offering Shares"), pursuant to the Subscription Right (as defined below).

The Rights are evidenced by non-transferable Rights certificates (the "Rights Certificates"). The number of Rights to which you are entitled is printed on the face of your Rights Certificate.

The Rights will expire if not exercised prior to 5:00 p.m., New York time, on March 2, 2020, unless extended by the Company (the "Expiration Time").

Each Recordholder will receive 0.152 Rights for each share of Common Stock, Series A Preferred Stock and Series B Preferred Stock owned of record by such Recordholder as of 5:00 p.m., New York time, on the Record Date. The total number of Rights issued to each Recordholder will be rounded down to the nearest whole number. Each whole Right allows the holder thereof to subscribe for one share of Common Stock at the cash price of \$9.00 per share (the "Subscription Price") (or an equivalent number of shares of Series C Preferred Stock on the terms described in the Prospectus) (the "Subscription Right"). Any holder that, following such exercise of such holder's Subscription Right, would be or become a holder of greater than 9.99% of the outstanding number of shares of the Common Stock may elect to instead purchase non-voting 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 in the Rights Offering.

Each holder of Rights will be required to submit payment in full to the Subscription Agent for all the Rights Offering Shares such holder of Rights wishes to buy pursuant to the exercise of its Subscription Right, which payment must be received by the Subscription Agent (and which payment must clear) prior to the Expiration Time.

The Company will not be required to issue Rights Offering Shares to you if the Subscription Agent does not receive your subscription payment (whether delivered directly if you are a Recordholder or indirectly through your broker, dealer, custodian bank or other nominee if you are a beneficial owner but not a Recordholder) prior to the Expiration Time, regardless of when you send the subscription payment and related documents. The Company may extend the Expiration Time by giving oral or written notice to the Subscription Agent prior to the Expiration Time. If the Company elects to extend the Expiration Time, it will issue a press release announcing such extension.

**YOUR RIGHTS CERTIFICATE AND SUBSCRIPTION PRICE PAYMENT FOR EACH RIGHT THAT IS EXERCISED PURSUANT TO THE SUBSCRIPTION RIGHT, INCLUDING FINAL CLEARANCE OF ANY CHECKS, MUST BE RECEIVED BY THE SUBSCRIPTION AGENT, PRIOR TO THE EXPIRATION TIME.**

---

ONCE A HOLDER OF RIGHTS HAS EXERCISED ITS SUBSCRIPTION RIGHT, SUCH EXERCISE MAY NOT BE REVOKED.

RIGHTS NOT EXERCISED PRIOR TO THE EXPIRATION TIME OF THE RIGHTS OFFERING WILL EXPIRE AND WILL BE OF NO VALUE.

**1. Method of Subscription – Exercise of Rights.**

To exercise Rights, complete your Rights Certificate and send the properly completed and executed Rights Certificate evidencing such Rights with any signatures required to be guaranteed so guaranteed, together with payment in full of the Subscription Price for each Rights Offering Share subscribed for pursuant to the Subscription Right, to the Subscription Agent, prior to the Expiration Time. Payment of the Subscription Price will be held in a segregated account to be maintained by the Subscription Agent.

All payments must be made in U.S. dollars for the full number of Rights Offering Shares being subscribed for by personal check payable to “Computershare Trust Company, N.A. (acting as subscription agent for Spero Therapeutics, Inc.)”

Payments will be deemed to have been received upon clearance of any uncertified check.

Please note that the funds paid by uncertified personal check may take five or more business days to clear. Accordingly, we urge you to make payment sufficiently in advance of the Expiration Time to ensure that such payment is received and clears by such date.

All Rights Certificates, payments of the Subscription Price and nominee holder certifications, to the extent applicable to your exercise of Rights, must be delivered by mail or overnight courier to the Subscription Agent as follows:

By Mail:

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

By Overnight Courier:

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

Delivery to an address other than the address above does not constitute valid delivery.

If you have any questions, require assistance regarding the method of exercising Rights or require additional copies of relevant documents, please contact the Information Agent, Alliance Advisors LLC, at 200 Broadacres Drive, 3rd Floor, Bloomfield, NJ 07003, or by phone at 800-574-6215.

By making arrangements with your bank or broker for the delivery of funds on your behalf, you may also request such bank or broker to exercise the Rights on your behalf.

Brokers, custodian banks and other nominee holders who exercise the Subscription Right on behalf of beneficial owners of Rights will be required to certify to the Subscription Agent and the Company as to the aggregate number of Rights that have been exercised pursuant to the Subscription Right by each beneficial owner of Rights (including such nominee itself) on whose behalf such nominee holder is acting.

---

If you do not indicate the number of Rights being exercised, or do not forward full payment of the Subscription Price for all of the Rights you purport to exercise, then you will be deemed to have exercised your Rights with respect to the maximum number of whole Rights that may be exercised with the aggregate amount of Subscription Price you delivered to the Subscription Agent.

If the Company does not apply your full Subscription Price payment to your purchase of Rights Offering Shares, the excess subscription payment received by the Subscription Agent will be returned to you, without interest or penalty, as soon as practicable.

## **2. Issuance of Rights Offering Shares.**

All Rights Offering Shares that you purchase in the Rights Offering will be issued in book-entry, or uncertificated, form. When issued, the Rights Offering Shares will be registered in the name of the Recordholder. As soon as practicable after the expiration of the Rights Offering (including after all prorrations and adjustments contemplated by the terms of the Rights Offering, as described in the Prospectus, have been effected), the Subscription Agent will arrange for the issuance of the Rights Offering Shares allotted to the holders exercising their Subscription Rights in the Rights Offering.

As soon as practicable after the Expiration Time and after all prorrations and adjustments contemplated by the terms of the Rights Offering, as described in the Prospectus, have been effected, any excess subscription payment received by the Subscription Agent will be returned, without interest or penalty.

## **3. Non-Transferability of Rights.**

The Rights are exercisable only by Recordholders, and you may not sell, transfer, assign or otherwise dispose of your Rights to anyone else.

## **4. Execution.**

(a) *Execution by Registered Holder.* The signature on the Rights Certificate must correspond with the name of the registered holder exactly as it appears on the face of the Rights Certificate without any alteration or change whatsoever. Persons who sign the Rights Certificate in a representative or other fiduciary capacity must indicate their capacity when signing and, unless waived by the Subscription Agent in its sole and absolute discretion, must present to the Subscription Agent satisfactory evidence of their authority to so act.

(b) *Execution by Person Other than Registered Holder.* If the Rights Certificate is executed by a person other than the holder named on the face of the Rights Certificate, proper evidence of authority of the person executing the Rights Certificate must accompany the same unless the Company, in its sole discretion, dispenses with proof of authority.

(c) *Signature Guarantees.* If you completed any portion of Form 2 of the Rights Certificate, your signature must be guaranteed by an eligible institution participating in the medallion guarantee program if you specify special delivery instructions.

## **5. Method of Delivery.**

The method of delivery of Rights Certificates and payment of the aggregate Subscription Price to the Subscription Agent will be at the election and risk of the holder of Rights. Payment by uncertified personal check will not be deemed to have been received by the Subscription Agent until the check has cleared. Any personal check used to pay for Rights Offering Shares must clear the appropriate financial institutions prior to the Expiration Time. The clearinghouse may require five or more business days. We urge you to make payment sufficiently in advance of the Expiration Time to ensure such payment is received and clears by such date.

---

**6. Determinations Regarding the Exercise of Your Rights.**

The Company will decide, in its sole discretion, all questions concerning the timeliness, validity, form and eligibility of the exercise of your Rights. Any such determinations by the Company will be final and binding. The Company, in its sole discretion, may waive, in any particular instance, any defect or irregularity or permit, in any particular instance, a defect or irregularity to be corrected within such time as the Company may determine. The Company will not be required to make uniform determinations in all cases. The Company may reject the exercise of any of your Rights because of any defect or irregularity.

The Company will not accept any exercise of Rights until all irregularities have been waived by the Company or cured by you within such time as the Company decides, in its sole discretion.

Neither the Company, the Subscription Agent nor the Information Agent will be under any duty to notify you of any defect or irregularity in connection with your submission of Rights Certificates, and none of them will be liable for failure to notify you of any defect or irregularity. The Company reserves the right to reject your exercise of Rights if the Company determines that your exercise is not in accordance with the terms of the Rights Offering, as set forth in the Prospectus and these Instructions as to Use, or in proper form. The Company will also not accept the exercise of your Rights if the Company's issuance of Rights Offering Shares to you could be deemed unlawful under applicable law.

**FORM OF LETTER TO RECORD HOLDERS****SPERO THERAPEUTICS, INC.**

## Subscription Rights to Purchase Shares of Common Stock

February 11, 2020

Dear Spero Stockholder:

This letter is being distributed by Spero Therapeutics, Inc. (the "Company") to all holders of record of shares of the Company's common stock, par value \$0.001 per share (the "Common Stock"), Series A convertible preferred stock, par value \$0.001 per share (the "Series A Preferred Stock"), and Series B convertible preferred stock, par value \$0.001 per share (the "Series B Preferred Stock"), as of 5:00 p.m., New York time, on February 10, 2020 (the "Record Date"), in connection with the distribution of non-transferable subscription rights (the "Rights") to such holders to subscribe for and purchase up to an aggregate of 3,333,333 shares of Common Stock in a rights offering (the "Rights Offering") for a subscription price of \$9.00 per share of Common Stock (the "Subscription Price"). Any holder that, following exercise of such holder's Subscription Right (as defined below) would be or become a holder of greater than 9.99% of the outstanding number of shares of the Common Stock may elect to instead purchase non-voting Series C convertible preferred stock, par value \$0.001 per share (the "Series C Preferred Stock"), at a subscription 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 in the Rights Offering. The Company is offering up to an aggregate of 3,333,333 shares of Common Stock and up to an aggregate of 3,333 shares of Series C Preferred Stock in the Rights Offering (the "Shares"). Holders as of the Record Date of the Company's Series A Preferred Stock and Series B Preferred Stock also will have a right to participate in the Rights Offering on an as-converted-to-Common Stock basis. The Rights and the Shares are described in the prospectus supplement (and the accompanying prospectus), dated February 11, 2020 (the "Prospectus"), covering the offer and sale of the Shares issuable upon the exercise of the Rights.

As described in the Prospectus, you will receive 0.152 Rights for each share of Common Stock owned of record by you, or issuable upon conversion of the shares of Series A Preferred Stock or Series B Preferred Stock of which you are a record holder, as of 5:00 p.m., New York time, on the Record Date. The Rights are evidenced by a non-transferable certificate (the "Rights Certificate") registered in your name and will cease to have any value as of 5:00 p.m., New York time, on March 2, 2020, unless the Rights Offering is extended by the Company as described below (the "Expiration Time"). The total number of Rights issued to you will be rounded down to the nearest whole number and 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 the Prospectus) (the "Subscription Right").

As further described in the Prospectus, the Company has entered into an Investment Agreement with BVF Partners L.P. and its affiliates ("BVF"), pursuant to which BVF has agreed to purchase from the Company any and all Shares not subscribed for in the Rights Offering, in the form of Series C Preferred Stock, as further described in the Prospectus. BVF also will have the same right as other stockholders to subscribe for and purchase Shares under its Subscription Right. The Investment Agreement with BVF is described in more detail in the Prospectus.

**The Rights will expire and be of no value if not exercised prior to the Expiration Time.**

You will be required to submit payment in full for all of the Shares you wish to purchase pursuant to the exercise of the Subscription Right prior to the Expiration Time.

As soon as practicable after the Expiration Time and after any and all prorations and adjustments contemplated by the terms of the Rights Offering, as described in the Prospectus, have been effected, any excess subscription payment received by Computershare Trust Company, N.A. (the "Subscription Agent") from you will be returned to you, without interest or penalty.

---

Enclosed are copies of the following documents:

1. **The Prospectus;**
2. **A Non-Transferable Subscription Rights Certificate evidencing the Rights for which you are the holder of record;**
3. **Instructions on how to Exercise the Spero Therapeutics, Inc. Rights Certificates; and**
4. **A return envelope addressed to Computershare Trust Company, N.A., the Subscription Agent.**

Your prompt action is requested. To exercise your Rights, you must promptly deliver the properly completed and signed Subscription Rights Certificate accompanying this letter, with payment of the Subscription Price in full for each Share subscribed pursuant to the Subscription Right to the Subscription Agent, as indicated in the Prospectus. **The Subscription Agent must receive the Rights Certificate with full payment of the Subscription Price, including final clearance of any checks, prior to the Expiration Time.**

You cannot revoke the exercise of your Rights. Rights not exercised prior to the Expiration Time will expire and be of no value.

Additional copies of the enclosed materials may be obtained from, and any questions or requests for assistance concerning the Rights Offering should be directed to, the Information Agent, Alliance Advisors LLC at 800-574-6215.

Very truly yours,

SPERO THERAPEUTICS, INC.

**FORM OF LETTER TO NOMINEES****SPERO THERAPEUTICS, INC.**

## Subscription Rights to Purchase Shares of Common Stock

February 11, 2020

To Securities Dealers, Commercial Banks

Trust Companies and Other Nominees:

This letter is being distributed to securities dealers, commercial banks, trust companies and other nominees in connection with a rights offering (the "Rights Offering") by Spero Therapeutics, Inc. (the "Company") to the holders of record (the "Recordholders") of its common stock, par value \$0.001 per share (the "Common Stock"), Series A convertible preferred stock, par value \$0.001 per share (the "Series A Preferred Stock"), and Series B convertible preferred stock, par value \$0.001 per share ("the Series B Preferred Stock"), as described in the prospectus supplement (and the accompanying prospectus) dated February 11, 2020 (the "Prospectus"). In the Rights Offering, Recordholders as of 5:00 p.m., New York time, on February 10, 2020 (the "Record Date"), are receiving, at no charge, non-transferable subscription rights (the "Rights") to subscribe for and purchase up to an aggregate of 3,333,333 shares of Common Stock (the "Shares") for a cash purchase price of \$9.00 per share of Common Stock (the "Subscription Price") pursuant to the Subscription Right (as defined below). Any holder, that following exercise of such holder's Subscription Right (as defined below), would be or become a holder of greater than 9.99% of the outstanding number of shares of the Common Stock may elect to instead purchase non-voting Series C convertible preferred stock, par value \$0.001 per share (the "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 in the Rights Offering.

The Rights will expire, if not exercised prior to 5:00 p.m., New York time, on March 2, 2020, unless extended by the Company (the "Expiration Time").

As described in the Prospectus, each beneficial owner of shares of Common Stock held through you or your nominee is entitled to 0.152 Subscription Rights for each share of Common Stock owned of record by you, or issuable upon conversion of the shares of the Company's Series A Preferred Stock or Series B Preferred Stock owned of record by you as of the Record Date. The total number of Rights issued will be rounded down to the nearest whole number. Each whole Right will allow the holder thereof 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 the Prospectus) (the "Subscription Right").

As further described in the Prospectus, the Company has entered into an Investment Agreement with BVF Partners L.P. and its affiliates ("BVF"), pursuant to which BVF has agreed to purchase from the Company any and all Shares not subscribed for in the Rights Offering, in the form of Series C Preferred Stock, as further described in the Prospectus. BVF also will have the same right as other stockholders to subscribe for and purchase Shares under its Subscription Right. The Investment Agreement with BVF is described in more detail in the Prospectus.

**The Rights will expire and be of no value, if not exercised prior to the Expiration Time.**

Each holder of Rights will be required to submit payment in full for all of the Shares such holder wishes to purchase pursuant to the exercise of the Subscription Right prior to the Expiration Time.

As soon as practicable after the Expiration Time and after any and all prorations and adjustments contemplated by the terms of the Rights Offering, as described in the Prospectus, have been effected, any excess subscription payment received by Computershare Trust Company, N.A. (the "Subscription Agent") will be returned, without interest or penalty.

---

The Company is asking persons who hold shares of Common Stock beneficially and who have received the Rights distributable with respect to those shares through a broker, dealer, commercial bank, trust company or other nominee, as well as persons who hold certificates of Common Stock directly and prefer to have such institutions effect transactions relating to the Rights on their behalf, to contact the appropriate institution or nominee and request it to effect the transactions for them.

All commissions, fees and other expenses (including brokerage commissions and transfer taxes), other than fees and expenses of the Subscription Agent, incurred in connection with the exercise of the Rights will be for the account of the holder of the Rights, and none of such commissions, fees or expenses will be paid by the Company or the Subscription Agent.

**Enclosed are copies of the following documents:**

1. **The Prospectus;**
2. **A form of letter which may be sent to your clients for whose accounts you hold shares of Common Stock registered in your name or Cede & Co. (including a Beneficial Owner Election Form), with an attached form of instruction; and**
3. **Nominee Holder Certification**

Your prompt action is requested. To exercise the Rights, you must promptly deliver the properly completed and signed Nominee Holder Certification accompanying this letter, with payment of the aggregate Subscription Price in full for each Share subscribed pursuant to the Subscription Right to the Subscription Agent, as indicated in the Prospectus. **The Subscription Agent must receive the Nominee Holder Certification with full payment of the Subscription Price, including final clearance of any checks, prior to the Expiration Time.**

A holder of Rights cannot revoke the exercise of such holder's Rights. Rights not exercised prior to the Expiration Time will expire and be of no value.

Additional copies of the enclosed materials may be obtained from Alliance Advisors LLC, which is serving as the Information Agent. Alliance Advisors LLC can be reached at 800-574-6215 in connection with requests for materials or questions or requests for assistance concerning the Rights Offering.

Very truly yours,

SPERO THERAPEUTICS, INC.

**FORM OF LETTER TO BENEFICIAL OWNERS**  
**SPERO THERAPEUTICS, INC.**

Subscription Rights to Purchase Shares of Common Stock

February 11, 2020

To Our Clients:

Enclosed for your consideration is a prospectus supplement (and the accompanying prospectus), dated February 11, 2020 (the "Prospectus"), that relates to the offering (the "Rights Offering") by Spero Therapeutics, Inc. (the "Company") of shares of its common stock, par value \$0.001 per share (the "Common Stock"), pursuant to the distribution of non-transferable subscription rights (the "Rights") to all holders of record of shares of Common Stock, holders of Series A convertible preferred stock, par value \$0.001 per share (the "Series A Preferred Stock"), and Series B convertible preferred stock, par value \$0.001 per share (the "Series B Preferred Stock") (collectively, the "Rights Offering Participants"), as of 5:00 p.m., New York time, on February 10, 2020 (the "Record Date"). In the Rights Offering, the Company is offering up to an aggregate of 3,333,333 shares of Common Stock and up to an aggregate of 3,333 shares of non-voting Series C convertible preferred stock, par value \$0.001 per share (the "Series C Preferred Stock") (collectively, the "Shares"), for a cash purchase price of \$9.00 per share of Common Stock (the "Subscription Price"), pursuant to the Subscription Right (as defined below). Any holder that, following exercise of such holder's Subscription Right (as defined below) would be or become a holder of greater than 9.99% of the outstanding number of shares of the Common Stock 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 in the Rights Offering.

As described in the Prospectus, you will receive 0.152 Rights for each share of Common Stock owned of record by you, or issuable upon conversion of the shares of Series A Preferred Stock or Series B Preferred Stock of which you are a record holder, as of 5:00 p.m., New York time, on the Record Date. The Rights are evidenced by a non-transferable certificate (the "Rights Certificate") registered in your name and will cease to have any value as of 5:00 p.m., New York time, on March 2, 2020, unless extended by the Company as described below (the "Expiration Time"). The total number of Rights issued to each stockholder will be rounded down to the nearest whole number and 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 the Prospectus) (the "Subscription Right").

As further described in the Prospectus, the Company has entered into an Investment Agreement with BVF Partners L.P. and its affiliates ("BVF"), pursuant to which BVF has agreed to purchase from the Company any and all Shares not subscribed for in the Rights Offering, in the form of Series C Preferred Stock, as further described in the Prospectus. BVF also will have the same right as other stockholders to subscribe for and purchase Shares under its Subscription Right. The Investment Agreement with BVF is described in more detail in the Prospectus.

**The Rights will expire and be of no value, if not exercised prior to the Expiration Time.**

You will be required to submit payment in full for all of the Shares you wish to purchase pursuant to the exercise of the Subscription Right prior to the Expiration Time.

As soon as practicable after the Expiration Time and after any and all prorations and adjustments contemplated by the terms of the Rights Offering, as described in the Prospectus, have been effected, any excess subscription payment received by Computershare Trust Company, N.A. (the "Subscription Agent") will be returned to you, without interest or penalty.

---

THE MATERIALS ENCLOSED ARE BEING FORWARDED TO YOU AS THE BENEFICIAL OWNER OF COMMON STOCK CARRIED BY US IN YOUR ACCOUNT BUT NOT REGISTERED IN YOUR NAME. EXERCISES AND SALES OF RIGHTS MAY BE MADE ONLY BY US AS YOUR BROKER, DEALER, CUSTODIAN BANK OR OTHER NOMINEE AND PURSUANT TO YOUR INSTRUCTIONS.

Accordingly, we request instructions as to whether you wish us to elect to subscribe for any Shares to which you are entitled pursuant to your Subscription Right on the terms and subject to the conditions set forth in the enclosed Prospectus. **However, we urge you to read the Prospectus carefully before instructing us to exercise your Rights.**

If you wish to have us, on your behalf, exercise the Rights for any Shares to which you are entitled, please so instruct us by completing, executing and returning to us the Beneficial Owner Election Form enclosed with this letter.

Your instructions to us should be forwarded as promptly as possible in order to permit us to exercise Rights on your behalf in the Rights Offering. **The Rights Offering will expire, and the Rights will not be exercisable and will have no value, at the Expiration Time. Once you have exercised the Subscription Right, such exercise may not be revoked.**

Additional copies of the enclosed materials may be obtained from Alliance Advisors LLC, 200 Broadacres Drive, 3rd Floor, Bloomfield, NJ 07003, the Information Agent for the Rights Offering. The Information Agent's telephone number is 800-574-6215. Any questions or requests for assistance concerning the Rights Offering should be directed to the Information Agent at the same number.

Very truly yours,

SPERO THERAPEUTICS, INC.

**BENEFICIAL OWNER ELECTION FORM**

The undersigned acknowledge(s) receipt of your letter and the enclosed materials relating to the grant of non-transferable subscription rights (the “Rights”) to subscribe for and to purchase shares of common stock, par value \$0.001 per share (the “Common Stock”), of Spero Therapeutics, Inc. (the “Company”) for a cash purchase price of \$9.00 per share. Any holder of greater than 9.99% of the outstanding number of shares of the Common Stock may elect to instead purchase non-voting Series C convertible preferred stock of the Company, par value \$0.001 per share (the “Series C Preferred Stock”), at a purchase price of \$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 in the Rights Offering, as described in the Prospectus.

**With respect to any instructions to exercise (or not to exercise) Rights, the undersigned acknowledges that this form must then be completed and returned such that it will actually be received by you by 5:00 p.m., New York time, on February 28, 2020, the last business day prior to the scheduled expiration date of the rights offering of March 2, 2020 (which may be extended by the Company).**

This will instruct you whether to exercise the Rights to purchase shares of Common Stock and/or Series C Preferred Stock distributed with respect to the shares of Common Stock, Series A convertible preferred stock of the Company, par value \$0.001 per share, and Series B convertible preferred stock of the Company, par value \$0.001 per share, held through you as broker, dealer, custodian bank or other nominee for the account of the undersigned, pursuant to the terms and subject to the conditions set forth in the prospectus supplement (and accompanying prospectus) dated **February 11, 2020** (the “Prospectus”), and the related “Instructions as to Use of Spero Therapeutics, Inc. Rights Certificates.”

I (we) hereby instruct you as follows:

(CHECK THE APPLICABLE BOXES AND PROVIDE ALL REQUIRED INFORMATION)

Box 1.  Please **DO NOT EXERCISE RIGHTS**.

Box 2.  Please **EXERCISE RIGHTS** as set forth below:

	<u>Number of Shares of Common Stock Subscribed For</u>		<u>Subscription Price</u>		<u>Payment</u>
Common Subscription Right		x	\$ 9.00	=	\$
	<u>Number of Shares of non-voting Series C Preferred Stock Subscribed For</u>		<u>Subscription Price</u>		<u>Payment</u>
Preferred Subscription Right (for holders that, following exercise of such holder’s subscription right (as described in the Prospectus), would be or become a holder of greater than 9.99% of the Company’s outstanding common shares):		x	\$ 9,000.00	=	\$

**If you are NOT a holder, or if following exercise of your subscription right, you would not be or become a holder of greater than 9.99% of the outstanding common shares and you apply to purchase shares of non-voting Series C Preferred Stock, you will not receive any, but will instead receive an equivalent number of shares of Common Stock (on an as-converted basis) in consideration for the same purchase price.**

---

Box 3.  Payment in the following amount is enclosed: \$\_\_\_\_\_

Box 4.  Please deduct payment of \$\_\_\_\_\_ from the following account maintained by you as follows:

(The total of Box 3 and Box 4 must equal the Total Payment Required specified above under Box 2.)

Type of Account \_\_\_\_\_ Account No. \_\_\_\_\_

I (we) on my (our) own behalf, or on behalf of any person(s) on whose behalf, or under whose directions, I am (we are) signing this form:

- irrevocably elect to purchase the number of shares of Common Stock and/or Series C Preferred Stock indicated above upon the terms and conditions specified in the Prospectus; and
- agree that if I (we) fail to pay for the shares of Common Stock and/or Series C Preferred Stock in full I (we) have elected to purchase pursuant to the exercise of the Subscription Right, you may exercise any remedies available to you under law.

Name of beneficial owner(s): \_\_\_\_\_

Signature of beneficial owner(s): \_\_\_\_\_

If you are signing in your capacity as a trustee, executor, administrator, guardian, attorney-in-fact, agent, officer of a corporation or another acting in a fiduciary or representative capacity, please provide the following information:

Name: \_\_\_\_\_

Capacity: \_\_\_\_\_

Address (including Zip Code): \_\_\_\_\_

Telephone Number: \_\_\_\_\_

**NOMINEE HOLDER CERTIFICATION  
SPERO THERAPEUTICS, INC.**

The undersigned, a broker, custodian bank, trustee, depository or other nominee holder of non-transferable subscription rights (the "Rights") to purchase shares of common stock, par value \$0.001 per share (the "Common Stock"), of Spero Therapeutics, Inc. (the "Company"), pursuant to the rights offering described and provided for in the Company's prospectus supplement (and the accompanying prospectus) dated February 11, 2020 (the "Prospectus"), hereby certifies to Computershare Trust Company, N.A., as subscription agent for the rights offering, that the undersigned has exercised, on behalf of the beneficial owners thereof (which may include the undersigned), the number of Rights specified below pursuant to the subscription right (as described in the Prospectus):

	<b>Number of Shares of Common Stock Owned (or issuable upon conversion of the shares of Series A Preferred Stock or Series B Preferred Stock) on the Record Date</b>	<b>Rights Exercised Pursuant to Subscription Right</b>
1.	_____	_____
2.	_____	_____
3.	_____	_____
4.	_____	_____
5.	_____	_____
6.	_____	_____
7.	_____	_____
8.	_____	_____
9.	_____	_____
10.	_____	_____

Note: Any holder that, following exercise of such holder's subscription right, would be or become a holder of greater than 9.99% of the outstanding number of shares of the Common Stock may elect to instead purchase non-voting Series C convertible preferred stock, par value \$0.001 per share (the "Series C Preferred Stock"), at a purchase price of \$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 in the Rights Offering.

---

Provide the following information if applicable:

\_\_\_\_\_  
Depository Trust Company (“DTC”)  
Participant Number

[NAME OF NOMINEE]

By: \_\_\_\_\_  
Name: \_\_\_\_\_  
Title: \_\_\_\_\_

DTC Basic Subscription Confirmation Number(s)

\_\_\_\_\_

**RIGHTS CERTIFICATE:**

**NUMBER OF RIGHTS:**

THE TERMS AND CONDITIONS OF THE RIGHTS OFFERING ARE SET FORTH IN THE COMPANY'S PROSPECTUS SUPPLEMENT (AND ACCOMPANYING PROSPECTUS) DATED FEBRUARY 11, 2020 (THE "PROSPECTUS") AND ARE INCORPORATED HEREIN BY REFERENCE. COPIES OF THE PROSPECTUS ARE AVAILABLE UPON REQUEST FROM ALLIANCE ADVISORS LLC, THE INFORMATION AGENT.

**Spero Therapeutics, Inc.**

**Incorporated under the laws of the State of Delaware**

**NON-TRANSFERABLE SUBSCRIPTION RIGHTS CERTIFICATE**

Evidencing Non-Transferable Subscription Rights to Purchase Shares of Common Stock of Spero Therapeutics, Inc.

Subscription Price: \$9.00 per Share

**THE SUBSCRIPTION RIGHTS WILL EXPIRE IF NOT EXERCISED ON OR BEFORE 5:00 P.M.,**

**NEW YORK TIME, ON MARCH 2, 2020, UNLESS EXTENDED BY THE COMPANY**

**COMPUTERSHARE ACCOUNT NUMBER:**

**REGISTERED OWNER:**

THIS CERTIFIES THAT the registered owner whose name is inscribed hereon is the owner of the number of non-transferable subscription rights ("Rights") set forth above. Each whole Right entitles the holder thereof to subscribe for and purchase one share of Common Stock, with a par value of \$0.001 per share (the "Common Stock"), of Spero Therapeutics, Inc., a Delaware corporation, at a subscription price of \$9.00 per share (the "Subscription Right"), pursuant to a rights offering (the "Rights Offering"), on the terms and subject to the conditions set forth in the Prospectus and the "Instructions as to Use of Spero Therapeutics, Inc. Subscription Rights Certificates" accompanying this Subscription Rights Certificate. As more fully described in the Prospectus, any holder, that following exercise of such holder's Subscription Right, would be or become a holder of more than 9.99% of the outstanding number of shares of the Common Stock may instead elect to instead purchase non-voting Series C convertible preferred stock, par value \$0.001 per share (the "Series C Preferred Stock"). The Rights represented by this Subscription Rights Certificate may be exercised by completing Form 1 and any other appropriate forms on the reverse side hereof and by returning the full payment of the subscription price for each share of Common Stock in accordance with the "Instructions as to Use of Spero Therapeutics, Inc. Subscription Rights Certificates" that accompany this Subscription Rights Certificate.

The Rights represented by this Subscription Rights Certificate may be exercised, as described further in the Prospectus, by delivering to Computershare Trust Company, N.A. ("Computershare" or the "Subscription Agent"), prior to 5:00 p.m., New York time, on the Expiration Date of March 2, 2020 (unless extended), with this Subscription Rights Certificate, properly completed and executed, together with full payment for all the Rights the holder elects to exercise under the Subscription Right. All Rights not exercised prior to 5:00 p.m., New York time, on March 2, 2020 shall be null and void.

This Subscription Rights Certificate is not valid unless signed by the registered owner.

DELIVERY OPTIONS FOR SUBSCRIPTION RIGHTS CERTIFICATE

Delivery other than by mail or overnight courier to the address listed below will not constitute valid delivery.

THE SUBSCRIPTION AGENT FOR THE OFFER IS:



By Mail:

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

By Overnight Courier:

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

PLEASE PRINT ALL INFORMATION CLEARLY AND LEGIBLY.

FORM 1-EXERCISE OF SUBSCRIPTION RIGHTS

To subscribe for shares pursuant to your Subscription Right, please complete line (a) OR (b) and sign under Form 3 below.

*\*To determine No. of shares of common stock in line (A), multiply the number of Rights you wish to exercise by 0.152 and round down to the nearest whole share of common stock.*

EXERCISE OF SUBSCRIPTION RIGHT:

(a) I apply for \_\_\_\_\_ shares x \$9.00 = \$ \_\_\_\_\_  
(no. of new shares) (subscription price) (amount enclosed)

(b) FOR HOLDERS, THAT FOLLOWING EXERCISE OF SUCH HOLDER'S SUBSCRIPTION RIGHT WOULD BE OR BECOME A HOLDER OF GREATER THAN 9.99% OF THE OUTSTANDING NUMBER OF SHARES OF COMMON STOCK:

I apply for \_\_\_\_\_ shares x \$9,000.00 = \$ \_\_\_\_\_  
(no. of new shares) (subscription price) (amount enclosed)

NOTE: If you are NOT a holder of, or if following exercise of your Subscription Right, you would not be or become a holder of greater than 9.99% of the outstanding shares of Common Stock and you apply to purchase shares of Series C Preferred Stock, you will not receive any, but will instead receive an equivalent number of shares of Common Stock (on an as-converted basis) in consideration for the same purchase price.

Payment: Full payment for the number of shares you wish to acquire through the Subscription Right must accompany this Subscription Rights Certificate. Payment must be delivered by personal check payable to the Subscription Agent, which payment must clear prior to the Expiration Date. **Please reference your rights card control number on your personal check.**

---

Check payable to "Computershare Trust Company, N.A. (acting as subscription agent for Spero Therapeutics, Inc.)"

**FORM 2-DELIVERY TO DIFFERENT ADDRESS**

Unless specifically requested, shares of Common Stock will be issued in book entry form. If you wish for the Common Stock underlying your subscription rights to be delivered to an address different from that shown on the face of this Subscription Rights Certificate, please enter the alternate address below, sign under Form 3 and have your signature guaranteed under Form 4. If your signature is not guaranteed, the shares will be issued to you in book entry form.

**FORM 3-SIGNATURE**

TO SUBSCRIBE: I acknowledge that I have received the Prospectus for this Rights Offering and I hereby irrevocably subscribe for the number of shares indicated above on the terms and conditions specified in the Prospectus. I agree to cooperate with the Company and provide to the Company any and all information requested by the Company in connection with the exercise of the rights granted in the previous sentence.

Print your name(s):

Signature(s):

Signature of Co-Owner (if more than one registered holder listed)

Date (mm/dd/yyyy): \_\_\_\_\_

IMPORTANT: The signature(s) must correspond with the name(s) as printed on the reverse of this Subscription Rights Certificate in every particular, without alteration or enlargement, or any other change whatsoever.

**FORM 4-SIGNATURE GUARANTEE**

This form must be completed if you have completed any portion of Form 2.

Signature Guaranteed: \_\_\_\_\_

(Name of Bank or Firm)

By: \_\_\_\_\_

(Signature of Officer)

IMPORTANT: The signature(s) should be guaranteed by an eligible guarantor institution (bank, stock broker, savings & loan association or credit union) with membership in an approved signature guarantee medallion program pursuant to Securities and Exchange Commission Rule 17Ad-15.

FOR INSTRUCTIONS ON THE USE OF SPERO THERAPEUTICS, INC. SUBSCRIPTION RIGHTS CERTIFICATES, CONSULT ALLIANCE ADVISORS LLC, 200 BROADACRES DRIVE, 3RD FLOOR, BLOOMFIELD, NJ 07003, THE INFORMATION AGENT, AT 800-574-6215.

## Spero Therapeutics Announces Commencement of Rights Offering

CAMBRIDGE, Mass., February 11, 2020 (GLOBE NEWSWIRE) — Spero Therapeutics, Inc. (Nasdaq: SPRO), a multi-asset clinical-stage biopharmaceutical company focused on identifying, developing and commercializing treatments in high unmet need areas involving multi-drug resistant bacterial infections and rare diseases, today commenced its previously announced rights offering to raise gross proceeds of \$30.0 million (the “Rights Offering”). Under the terms of the Rights Offering, holders of record of Spero’s common stock (“Common Stock”), Series A convertible preferred stock (“Series A Preferred”) and Series B convertible preferred stock (“Series B Preferred”) as of 5:00 p.m., New York time, on February 10, 2020 (the “Record Date”) will receive non-transferable subscription rights entitling them to purchase up to an aggregate of 3,333,333 shares of Common Stock at a subscription price equal to \$9.00 per share in proportion to their respective pro rata ownership of Common Stock outstanding (assuming the conversion of all outstanding Series A Preferred and Series B Preferred into shares of Common Stock), or, under certain circumstances, shares of non-voting Series C convertible preferred stock (“Series C Preferred”) in lieu of Common Stock (collectively, the “Offered Shares”), as more fully described in the prospectus supplement, dated February 11, 2020, relating to the Rights Offering. The subscription rights may be exercised any time during the subscription period of February 11, 2020 through 5:00 p.m., New York time, on March 2, 2020.

The Rights Offering will be fully backstopped by certain affiliates of BVF Partners L.P. (“BVF”), which have agreed to purchase, at a minimum, their respective as-converted pro rata share of the Offered Shares, plus an additional amount of Common Stock or Series C Preferred that are not subscribed for by other purchasers in the Rights Offering, for a total of up to \$30.0 million. Spero expects to use the proceeds from the Rights Offering 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.

Spero reserves the right to extend or cancel the Rights Offering at any time prior to the closing of the sale of the Offered Shares in the Rights Offering. Spero has engaged Alliance Advisors LLC to act as information agent with respect to the Rights Offering. For questions regarding the Rights Offering, or to obtain copies of the Rights Offering prospectus supplement and any related materials, please contact Alliance Advisors LLC at [reorg@allianceadvisorsllc.com](mailto:reorg@allianceadvisorsllc.com) or by telephone at 800-574-6215.

Spero has filed a shelf registration statement (including a prospectus supplement) with the Securities and Exchange Commission (the “SEC”) (File No. 228661). Before you invest, you should read the prospectus supplement and other documents Spero has filed with the SEC for more complete information about Spero and the Rights Offering. This press release is not intended to and does not constitute an offer to sell or the solicitation of an offer to subscribe for or buy or an invitation to purchase or subscribe for any securities in any jurisdiction, nor shall there be any sale, issuance or transfer of securities in any jurisdiction in contravention of applicable law.

---

## About Spero

Spero Therapeutics, Inc. is a multi-asset, clinical-stage biopharmaceutical company focused on identifying, developing and commercializing novel treatments for multidrug-resistant (MDR) bacterial infections and rare diseases.

Spero's lead product candidate, tebipenem HBr (tebipenem pivoxil hydrobromide; formerly SPR994), is designed to be the first oral carbapenem-class antibiotic for use in adults to treat MDR Gram-negative infections.

Spero is also advancing SPR720, its novel oral therapy product candidate designed for the treatment of rare, orphan disease caused by pulmonary non-tuberculous mycobacterial (NTM) infections.

Spero also has a platform technology known as its Potentiator Platform that it believes will enable it to develop drugs that will expand the spectrum and potency of existing antibiotics, including formerly inactive antibiotics, against Gram-negative bacteria. Spero's potentiator product candidate, SPR206, is designed to treat MDR Gram-negative infections in the hospital setting.

For more information, visit <https://sperotherapeutics.com>.

## Forward Looking Statement

Investors are cautioned that statements in this press release regarding the intention, completion and timing relating to the rights offering, the intended use of proceeds from the rights offering and Spero's future development plans for its product candidates and the timing and costs thereof constitute forward-looking statements that involve risks and uncertainties, including, without limitation, risks and uncertainties related to market conditions and the satisfaction of customary closing conditions related to the rights offering and the uncertainties inherent in the research and clinical development process. Additional information on risks facing Spero can be found under the heading "Risk Factors" in Spero's periodic reports, including its annual report on Form 10-K and quarterly reports on Form 10-Q, and in the preliminary prospectus relating to the offering filed with the SEC, each available on the SEC's web site at [www.sec.gov](http://www.sec.gov). Spero expressly disclaims any obligation or undertaking to release publicly any updates or revisions to any forward-looking statements contained herein to reflect any change in its expectations with regard thereto or any change in events, conditions or circumstances on which any such statements are based.

## Spero Investor and Media Contact:

Sharon Klahre  
Senior Director, Investor Relations  
857-242-1547  
[IR@sperotherapeutics.com](mailto:IR@sperotherapeutics.com)