

INITIAL STATEMENT OF BENEFICIAL OWNERSHIP OF SECURITIES

OMB APPROVAL

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hours per response: 0.5Filed pursuant to Section 16(a) of the Securities Exchange Act of 1934
or Section 30(h) of the Investment Company Act of 1940

1. Name and Address of Reporting Person* <u>Keutzer Timothy</u> (Last) (First) (Middle) <u>C/O SPERO THERAPEUTICS, INC.</u> <u>675 MASSACHUSETTS AVENUE, 14TH FLOOR</u> (Street) <u>CAMBRIDGE MA 02139</u> (City) (State) (Zip)	2. Date of Event Requiring Statement (Month/Day/Year) <u>01/01/2020</u>	3. Issuer Name and Ticker or Trading Symbol <u>Spero Therapeutics, Inc. [SPRO]</u>	
		4. Relationship of Reporting Person(s) to Issuer (Check all applicable) Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) <u>Chief Development Officer</u>	5. If Amendment, Date of Original Filed (Month/Day/Year) 6. Individual or Joint/Group Filing (Check Applicable Line) <input checked="" type="checkbox"/> Form filed by One Reporting Person Form filed by More than One Reporting Person

Table I - Non-Derivative Securities Beneficially Owned

1. Title of Security (Instr. 4)	2. Amount of Securities Beneficially Owned (Instr. 4)	3. Ownership Form: Direct (D) or Indirect (I) (Instr. 5)	4. Nature of Indirect Beneficial Ownership (Instr. 5)
<u>Common Stock</u>	<u>2,500⁽¹⁾</u>	<u>D</u>	

Table II - Derivative Securities Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)

1. Title of Derivative Security (Instr. 4)	2. Date Exercisable and Expiration Date (Month/Day/Year)		3. Title and Amount of Securities Underlying Derivative Security (Instr. 4)	4. Conversion or Exercise Price of Derivative Security	5. Ownership Form: Direct (D) or Indirect (I) (Instr. 5)	6. Nature of Indirect Beneficial Ownership (Instr. 5)
	Date Exercisable	Expiration Date				
<u>Stock Option (Right to Buy)</u>	<u>(2)</u>	<u>07/05/2027</u>	<u>Common Stock</u>	<u>10,695⁽³⁾</u>	<u>5.9⁽³⁾</u>	<u>D</u>
<u>Stock Option (Right to Buy)</u>	<u>(4)</u>	<u>07/05/2027</u>	<u>Common Stock</u>	<u>7,311⁽³⁾</u>	<u>5.9⁽³⁾</u>	<u>D</u>
<u>Stock Option (Right to Buy)</u>	<u>(5)</u>	<u>07/05/2027</u>	<u>Common Stock</u>	<u>987⁽³⁾</u>	<u>5.9⁽³⁾</u>	<u>D</u>
<u>Stock Option (Right to Buy)</u>	<u>(6)</u>	<u>07/05/2027</u>	<u>Common Stock</u>	<u>36,950⁽³⁾</u>	<u>5.9⁽³⁾</u>	<u>D</u>
<u>Stock Option (Right to Buy)</u>	<u>(7)</u>	<u>12/12/2027</u>	<u>Common Stock</u>	<u>25,016</u>	<u>11.63</u>	<u>D</u>
<u>Stock Option (Right to Buy)</u>	<u>(8)</u>	<u>01/02/2029</u>	<u>Common Stock</u>	<u>25,000</u>	<u>6.26</u>	<u>D</u>

Explanation of Responses:

- Reflects shares that were purchased through a directed share program in connection with the Issuer's initial public offering.
- All shares underlying this option are fully vested.
- The number of underlying shares of common stock and the exercise price reported reflect a 1-for-6.0774 reverse stock split of the Issuer's common stock effected on October 20, 2017.
- The shares underlying this option vested as to 25% on April 28, 2017, with the remainder vesting in 36 equal monthly installments thereafter, subject to the Reporting Person's continued service through the applicable vesting date.
- All shares underlying this option are fully vested.
- The shares underlying this option vested as to 25% on July 6, 2018, with the remainder vesting in 36 equal monthly installments thereafter, subject to the Reporting Person's continued service through the applicable vesting date.
- The shares underlying this option vested as to 25% on December 13, 2018, with the remainder vesting in 36 equal monthly installments thereafter, subject to the Reporting Person's continued service through the applicable vesting date.
- The shares underlying this option vested as to 25% on January 2, 2020, with the remainder vesting in 36 equal monthly installments thereafter, subject to the Reporting Person's continued service through the applicable vesting date.

Remarks:

Exhibit 24.1 - Power of Attorney

/s/ Brian J. Shea, Attorney-in-Fact for Timothy Keutzer 01/13/2020

** Signature of Reporting Person Date

Reminder: Report on a separate line for each class of securities beneficially owned directly or indirectly.

* If the form is filed by more than one reporting person, see Instruction 5 (b)(v).

** Intentional misstatements or omissions of facts constitute Federal Criminal Violations See 18 U.S.C. 1001 and 15 U.S.C. 78ff(a).

Note: File three copies of this Form, one of which must be manually signed. If space is insufficient, see Instruction 6 for procedure.

Persons who respond to the collection of information contained in this form are not required to respond unless the form displays a currently valid OMB Number.

POWER OF ATTORNEY

Know all by these present, that the undersigned hereby constitutes and appoints each of Ankit Mahadevia, Chief Executive Officer and President of Spero Therapeutics, Inc. (the "Company"), Bethany Calagione of the Company, and Matthew J. Gardella, Matthew W. Tikonoff, Brian J. Shea, Samantha M. Silver, Anne T. Leland, Brenda L. Meyette and Jacquelyn Cannata of Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., signing singly, with full power of substitution, the undersigned's true and lawful attorney-in-fact to:

- (1) execute for and on behalf of the undersigned, forms and authentication documents for EDGAR Filing Access;
- (2) do and perform any and all acts for and on behalf of the undersigned which may be necessary or desirable to complete and execute any such forms and authentication documents;
- (3) execute for and on behalf of the undersigned, in the undersigned's capacity as an officer, director and/or 10% shareholder of the Company, Forms 3, 4 and 5 in accordance with Section 16(a) of the Securities Exchange Act of 1934 and the rules thereunder;
- (4) do and perform any and all acts for and on behalf of the undersigned which may be necessary or desirable to complete and execute any such Form 3, 4 or 5 and timely file such form with the United States Securities and Exchange Commission and any stock exchange or similar authority; and
- (5) take any other action of any type whatsoever in connection with the foregoing which, in the opinion of such attorney-in-fact, may be of benefit to, in the best interests of, or legally required by the undersigned, it being understood that the documents executed by such attorney-in-fact on behalf of the undersigned pursuant to this Power of Attorney shall be in such form and shall contain such terms and conditions as such attorney-in-fact may approve in such attorney-in-fact's discretion.

The undersigned hereby grants to each such attorney-in-fact full power and authority to do and perform any and every act and thing whatsoever requisite, necessary, or proper to be done in the exercise of any of the rights and powers herein granted, as fully to all intents and purposes as the undersigned might or could do if personally present, with full power of substitution or revocation, hereby ratifying and confirming all that such attorney-in-fact, or such attorney-in-fact's substitute or substitutes, shall lawfully do or cause to be done by virtue of this power of attorney and the rights and powers herein granted. The undersigned acknowledges that the foregoing attorneys-in-fact, in serving in such capacity at the request of the undersigned, are not assuming, nor is the Company assuming, any of the undersigned's responsibilities to comply with Section 16 of the Securities Exchange Act of 1934, as amended.

This Power of Attorney shall remain in full force and effect until the undersigned is no longer required to file Forms 3, 4 and 5 with respect to the undersigned's holdings of and transactions in securities issued by the Company, unless earlier revoked by the undersigned in a signed writing delivered to the foregoing attorneys-in-fact.

IN WITNESS WHEREOF, the undersigned has caused this Power of Attorney to be executed this 23rd day of December, 2019

/s/ Timothy Keutzer

Signature

Timothy Keutzer

Print Name