

OMB APPROVAL	
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**STATEMENT OF CHANGES IN BENEFICIAL OWNERSHIP**

Check this box if no longer subject to Section 16. Form 4 or Form 5 obligations may continue. See Instruction 1(b).

Filed 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* <b>Mahadevia Ankit</b>  (Last) (First) (Middle) <b>C/O SPERO THERAPEUTICS, INC.</b> <b>675 MASSACHUSETTS AVENUE, 14TH FLOOR</b>  (Street) <b>CAMBRIDGE MA 02139</b>  (City) (State) (Zip)	2. Issuer Name and Ticker or Trading Symbol <b>Spero Therapeutics, Inc. [ SPRO ]</b>	5. Relationship of Reporting Person(s) to Issuer (Check all applicable) <input checked="" type="checkbox"/> Director 10% Owner <input checked="" type="checkbox"/> Officer (give title below) Other (specify below) <b>CEO and President</b>
	3. Date of Earliest Transaction (Month/Day/Year) <b>12/27/2021</b>	
	4. If Amendment, Date of Original Filed (Month/Day/Year)	

**Table I - Non-Derivative Securities Acquired, Disposed of, or Beneficially Owned**

1. Title of Security (Instr. 3)	2. Transaction Date (Month/Day/Year)	2A. Deemed Execution Date, if any (Month/Day/Year)	3. Transaction Code (Instr. 8)		4. Securities Acquired (A) or Disposed Of (D) (Instr. 3, 4 and 5)			5. Amount of Securities Beneficially Owned Following Reported Transaction(s) (Instr. 3 and 4)	6. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	7. Nature of Indirect Beneficial Ownership (Instr. 4)
			Code	V	Amount	(A) or (D)	Price			
Common Stock	12/27/2021		M <sup>(1)</sup>		8,000	A	\$5.9	152,036 <sup>(2)</sup>	D	
Common Stock	12/27/2021		S <sup>(1)</sup>		8,000	D	\$14.5833 <sup>(3)</sup>	144,036 <sup>(2)</sup>	D	

**Table II - Derivative Securities Acquired, Disposed of, or Beneficially Owned (e.g., puts, calls, warrants, options, convertible securities)**

1. Title of Derivative Security (Instr. 3)	2. Conversion or Exercise Price of Derivative Security	3. Transaction Date (Month/Day/Year)	3A. Deemed Execution Date, if any (Month/Day/Year)	4. Transaction Code (Instr. 8)				6. Date Exercisable and Expiration Date (Month/Day/Year)		7. Title and Amount of Securities Underlying Derivative Security (Instr. 3 and 4)	8. Price of Derivative Security (Instr. 5)	9. Number of derivative Securities Beneficially Owned Following Reported Transaction(s) (Instr. 4)	10. Ownership Form: Direct (D) or Indirect (I) (Instr. 4)	11. Nature of Indirect Beneficial Ownership (Instr. 4)	
				Code	V	(A)	(D)	Date Exercisable	Expiration Date						Title
Stock Option (Right to Buy)	\$5.9	12/27/2021		M			8,000	(4)	07/05/2027	Common Stock	8,000	\$0.00	486,809	D	

**Explanation of Responses:**

- All transactions reported on this Form 4 were made pursuant to a previously adopted Rule 10b5-1 trading plan. Specifically, the transactions reported herein relate to option exercises and related sales (totaling 8,000 shares).
- Amount includes 65,817 shares of common stock held by the Mahadevia-Mehta Family Trust, of which the Reporting Person is a trustee. Amount also includes 78,219 restricted stock units ("RSUs") held by the Reporting Person. Each RSU represents the right to receive one share of common stock upon vesting. The RSUs vest in four equal annual installments beginning on August 26, 2022, subject to the Reporting Person's continued service through the applicable vesting date.
- The price reflected is the weighted-average sale price for shares sold. The shares were sold in multiple transactions and the range of sale prices for the transactions reported was \$14.25 to \$14.77 per share. The Reporting Person undertakes to provide to the issuer, any security holder of the issuer, or the staff of the Securities and Exchange Commission, upon request, full information regarding the number of shares sold at each separate price.
- All of the option exercises reported herein were made with respect to options granted pursuant to the Company's 2017 Equity Incentive Plan on July 6, 2017 with vesting schedules generally consisting of 25% cliff vesting on specified dates and 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/ Tamara Joseph, Attorney-in-Fact for Ankit Mahadevia 12/29/2021

\*\* 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 4 (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 Satyavrat Shukla, Tamara Joseph, and Meghan Small of Spero Therapeutics, Inc. (the "Company"), and Mathew J. Gardella and Matthew W. Tikonoff 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 and 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 option 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 holding 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 on this 10th day of September, 2021.

/s/ Ankit Mahadevia

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Ankit Mahadevia, MD