

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* <u>ORBIMED ADVISORS LLC</u> (Last) (First) (Middle) 601 LEXINGTON AVENUE 54TH FLOOR (Street) NEW YORK NY 10022-4629 (City) (State) (Zip)	2. Issuer Name and Ticker or Trading Symbol <u>ALPINE IMMUNE SCIENCES, INC.</u> [ALPN]	5. Relationship of Reporting Person(s) to Issuer (Check all applicable) <input checked="" type="checkbox"/> Director <input checked="" type="checkbox"/> 10% Owner Officer (give title below) Other (specify below)
	3. Date of Earliest Transaction (Month/Day/Year) 12/28/2020	
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	12/28/2020		S		600,000 ⁽¹⁾	D	\$14.25	3,070,955	I	See Footnotes ⁽²⁾⁽³⁾

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)					

1. Name and Address of Reporting Person*
ORBIMED ADVISORS LLC
 (Last) (First) (Middle)
 601 LEXINGTON AVENUE
 54TH FLOOR
 (Street)
 NEW YORK NY 10022-4629
 (City) (State) (Zip)

1. Name and Address of Reporting Person*
OrbiMed Capital GP VI LLC
 (Last) (First) (Middle)
 601 LEXINGTON AVENUE, 54TH FLOOR
 (Street)
 NEW YORK NY 10022
 (City) (State) (Zip)

Explanation of Responses:

- These shares of the Issuer's common stock ("Shares") were sold in a block order at a price of \$14.25.
- The Shares are held of record by OrbiMed Private Investments VI, LP ("OPI VI"). OrbiMed Capital GP VI LLC ("GP VI") is the general partner of OPI VI and OrbiMed Advisors LLC ("OrbiMed Advisors") is the managing member of OrbiMed GP VI. OrbiMed GP VI and OrbiMed Advisors may be deemed to have voting and investment power over the securities held by OPI VI and may be deemed to have beneficial ownership over such securities. OrbiMed Advisors exercises voting and investment power through a management committee comprised of Carl L. Gordon, Sven H. Borho, and Jonathan T. Silverstein, each of whom disclaims beneficial ownership of the Shares held by OPI VI.
- This report on Form 4 is filed by OrbiMed Advisors and OrbiMed GP VI. Each of the Reporting Persons disclaims beneficial ownership of the securities reported herein for purposes of Rule 16a-1(a) under the Securities Exchange Act of 1934, as amended (the "Exchange Act"), except to the extent of its pecuniary interest therein, if any. The Reporting Persons have designated Peter A. Thompson, an

employee of OrbiMed Advisors, to serve on the Issuer's board of directors. This report on Form 4 shall not be deemed an admission that any of the Reporting Persons, or Peter A. Thompson, is a beneficial owner of such securities for the purpose of Section 16 of the Exchange Act, or for any other purpose.

/s/ Jonathan Silverstein,
Member of OrbiMed Advisors 12/30/2020
LLC

/s/ Jonathan Silverstein,
Member of OrbiMed Capital 12/30/2020
GP VI LLC

** 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.