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

SCHEDULE 13D
Under the Securities Exchange Act of 1934
(Amendment No. 5)*

Alpine Immune Sciences, Inc.
(Name of Issuer)

Common Stock, par value \$0.001 per share

(Title of Class of Securities)

02083G100
(CUSIP Number)

OrbiMed Advisors LLC
OrbiMed Capital GP VI LLC
OrbiMed Genesis GP LLC

601 Lexington Avenue, 54th Floor
New York, NY 10022
Telephone: (212) 739-6400

(Name, Address and Telephone Number of Person
Authorized to Receive Notices and Communications)

November 10, 2021

(Date of Event Which Requires Filing of this Statement)

If the filing person has previously filed a statement on Schedule 13G to report the acquisition that is the subject of this Schedule 13D, and is filing this schedule because of § 240.13d-1(e), 240.13d-1(f) or 240.13d-1(g), check the following box .

Note: Schedules filed in paper format shall include a signed original and five copies of the schedule, including all exhibits. See § 240.13d-7(b) for other parties to whom copies are to be sent.

*The remainder of this cover page shall be filled out for a reporting person's initial filing on this form with respect to the subject class of securities, and for any subsequent amendment containing information which would alter disclosures provided in a prior cover page.

The information required on the remainder of this cover page shall not be deemed to be "filed" for the purpose of Section 18 of the Securities Exchange Act of 1934 ("Act") or otherwise subject to the liabilities of that section of the Act but shall be subject to all other provisions of the Act (however, see the Notes).

SCHEDULE 13D

CUSIP No. 02083G100		
1	NAME OF REPORTING PERSONS OrbiMed Advisors LLC	
2	CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP (See Instructions) (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
3	SEC USE ONLY	
4	SOURCE OF FUNDS (See Instructions) AF	
5	CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEMS 2(d) or 2(e) <input type="checkbox"/>	
6	CITIZENSHIP OR PLACE OF ORGANIZATION Delaware	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	SOLE VOTING POWER 0
	8	SHARED VOTING POWER 4,226,843 (1)
	9	SOLE DISPOSITIVE POWER 0
	10	SHARED DISPOSITIVE POWER 4,226,843 (1)
11	AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON 4,226,843 (1)	
12	CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES (See Instructions) <input type="checkbox"/>	
13	PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11) 14.4% (2)	
14	TYPE OF REPORTING PERSON (See Instructions) IA	

(1) Evidenced by (i) 4,081,592 shares of common stock (“Shares”) outstanding of Alpine Immune Sciences, Inc. (the “Issuer”) and (ii) 145,251 Shares issuable upon the exercise of warrants to purchase Shares (the “Warrants”).

(2) This percentage is calculated based on (i) 29,220,176 Shares outstanding as set forth in the Issuer’s Quarterly Report on Form 10-Q, filed with the Securities and Exchange Commission on November 10, 2021, and (ii) 145,251 Shares subject to currently exercisable Warrants.

SCHEDULE 13D

CUSIP No. 02083G100		
1	NAME OF REPORTING PERSONS OrbiMed Capital GP VI LLC	
2	CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP (See Instructions) (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
3	SEC USE ONLY	
4	SOURCE OF FUNDS (See Instructions) AF	
5	CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEMS 2(d) or 2(e) <input type="checkbox"/>	
6	CITIZENSHIP OR PLACE OF ORGANIZATION Delaware	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	SOLE VOTING POWER 0
	8	SHARED VOTING POWER 3,801,312 (1)
	9	SOLE DISPOSITIVE POWER 0
	10	SHARED DISPOSITIVE POWER 3,801,312 (1)
11	AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON 3,801,312 (1)	
12	CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES (See Instructions) <input type="checkbox"/>	
13	PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11) 12.9% (2)	
14	TYPE OF REPORTING PERSON (See Instructions) OO	

(1) Evidenced by (i) 3,656,061 shares of common stock ("Shares") outstanding of Alpine Immune Sciences, Inc. (the "Issuer") and (ii) 145,251 Shares issuable upon the exercise of warrants to purchase Shares (the "Warrants").

(2) This percentage is calculated based on (i) 29,220,176 Shares outstanding as set forth in the Issuer's Quarterly Report on Form 10-Q, filed with the Securities and Exchange Commission on November 10, 2021, and (ii) 145,251 Shares subject to currently exercisable Warrants.

SCHEDULE 13D

CUSIP No. 02083G100		
1	NAME OF REPORTING PERSONS OrbiMed Genesis GP LLC	
2	CHECK THE APPROPRIATE BOX IF A MEMBER OF A GROUP (See Instructions) (a) <input type="checkbox"/> (b) <input type="checkbox"/>	
3	SEC USE ONLY	
4	SOURCE OF FUNDS (See Instructions) AF	
5	CHECK BOX IF DISCLOSURE OF LEGAL PROCEEDINGS IS REQUIRED PURSUANT TO ITEMS 2(d) or 2(e) <input type="checkbox"/>	
6	CITIZENSHIP OR PLACE OF ORGANIZATION Delaware	
NUMBER OF SHARES BENEFICIALLY OWNED BY EACH REPORTING PERSON WITH	7	SOLE VOTING POWER 0
	8	SHARED VOTING POWER 425,531 (1)
	9	SOLE DISPOSITIVE POWER 0
	10	SHARED DISPOSITIVE POWER 425,531 (1)
11	AGGREGATE AMOUNT BENEFICIALLY OWNED BY EACH REPORTING PERSON 425,531 (1)	
12	CHECK BOX IF THE AGGREGATE AMOUNT IN ROW (11) EXCLUDES CERTAIN SHARES (See Instructions) <input type="checkbox"/>	
13	PERCENT OF CLASS REPRESENTED BY AMOUNT IN ROW (11) 1.5% (2)	
14	TYPE OF REPORTING PERSON (See Instructions) OO	

(1) Evidenced by (i) 425,531 shares of common stock ("Shares") outstanding of Alpine Immune Sciences, Inc. (the "Issuer").

(2) This percentage is calculated based on 29,220,176 Shares outstanding as set forth in the Issuer's Quarterly Report on Form 10-Q, filed with the Securities and Exchange Commission on November 10, 2021.

Item 1. Security and Issuer

This Amendment No. 5 (“Amendment No. 5”) to Schedule 13D supplements and amends the Statement on Schedule 13D of OrbiMed Advisors LLC and OrbiMed Capital GP VI LLC (the “Statement”) originally filed with the Securities and Exchange Commission (the “SEC”) on August 3, 2017, and amended by Amendment No. 1 thereto filed with the SEC on January 25, 2018, and Amendment No. 2 thereto filed with the SEC on January 23, 2019, Amendment No. 3 filed with the SEC on July 30, 2020, and Amendment No. 4 thereto filed with the SEC on December 30, 2020 (“Amendment No. 4”). The Statement relates to the common stock, par value \$0.001 per share (the “Shares”), of Alpine Immune Sciences, Inc., a Delaware corporation (the “Issuer”), with its principal offices located at 201 Elliott Avenue West, Suite 230, Seattle, WA 98119. The Shares are listed on the NASDAQ Global Market under the ticker symbol “ALPN”. Information given in response to each item shall be deemed incorporated by reference in all other items, as applicable.

This Amendment No. 5 is being filed to report that the beneficial ownership of the outstanding Shares held by the Reporting Persons was increased by more than 1% since Amendment No. 4 following the transactions described in Item 5(c) below.

Item 2. Identity and Background

(a) This Statement is being filed by OrbiMed Advisors LLC (“Advisors”), a limited liability company organized under the laws of Delaware, and OrbiMed Capital GP VI LLC (“GP VI”), a limited liability company organized under the laws of Delaware, and OrbiMed Genesis GP LLC (“OrbiMed Genesis”), a limited liability company organized under the laws of Delaware (collectively, the “Reporting Persons”).

(b) — (c), (f) OrbiMed Advisors, a limited liability company organized under the laws of Delaware and a registered investment adviser under the Investment Advisers Act of 1940, as amended, is the managing member of GP VI and OrbiMed Genesis, as more particularly described in Item 6 below. OrbiMed Advisors has its principal offices at 601 Lexington Avenue, 54th Floor, New York, New York 10022.

GP VI, a limited liability company organized under the laws of Delaware, is the general partner of OrbiMed Private Investments VI, LP (“OPI VI”), a limited partnership organized under the laws of Delaware, as more particularly described in Item 6 below. GP VI has its principal offices at 601 Lexington Avenue, 54th Floor, New York, New York 10022.

OrbiMed Genesis, a limited liability company organized under the laws of Delaware, is the general partner of OrbiMed Genesis Master, L.P. (“Genesis Master Fund”), a limited partnership organized under the laws of the Cayman Islands, as more particularly described in Item 6 below. OrbiMed Genesis has its principal offices at 601 Lexington Avenue, 54th Floor, New York, New York 10022.

The directors and executive officers of Advisors, GP VI, and OrbiMed Genesis are set forth on Schedules I, II, and III, attached hereto. Schedules I, II, and III set forth the following information with respect to each such person:

- (i) name;
- (ii) business address;
- (iii) present principal occupation or employment and the name, principal business and address of any corporation or other organization in which such employment is conducted; and
- (iv) citizenship.

(d) – (e) During the last five years, neither the Reporting Persons nor any person named in Schedule I, II, or III have been (i) convicted in a criminal proceeding (excluding traffic violations or similar misdemeanors) or (ii) a party to a civil proceeding of a judicial or administrative body of competent jurisdiction and as a result of such proceeding was or is subject to a judgment, decree or final order enjoining future violations of, or prohibiting or mandating activities subject to, federal or state securities laws or finding any violation with respect to such laws.

Item 3. Source and Amount of Funds or Other Consideration

The source of funds for the purchases described in Item 5(c) was the working capital of OPI VI and Genesis Master Fund.

Item 4. Purpose of Transaction

The Reporting Persons caused OPI VI and Genesis Master Fund to acquire Shares, and OPI VI to acquire warrants to purchase Shares (“Warrants”), for the purpose of making an investment in the Issuer and not with the intention of acquiring control of the Issuer’s business on behalf of OPI VI and Genesis Master Fund.

The Reporting Persons from time to time intend to review their investment in the Issuer on the basis of various factors, including the Issuer’s business, financial condition, results of operations and prospects, general economic and industry conditions, the securities markets in general and those for the Issuer’s Shares in particular, as well as other developments and other investment opportunities. Based upon such review, the Reporting Persons will take such actions in the future as the Reporting Persons may deem appropriate in light of the circumstances existing from time to time. If the Reporting Persons believe that further investment in the Issuer is attractive, whether because of the market price of the Shares or otherwise, they may acquire Shares or other securities of the Issuer either in the open market or in privately negotiated transactions. Similarly, depending on market and other factors, the Reporting Persons may determine to dispose of some or all of the Shares currently owned by the Reporting Persons or otherwise acquired by the Reporting Persons either in the open market or in privately negotiated transactions.

Except as set forth in this Amendment No. 4, the Reporting Persons have not formulated any plans or proposals which relate to or would result in: (a) the acquisition by any person of additional securities of the Issuer or the disposition of securities of the Issuer; (b) an extraordinary corporate transaction, such as a merger, reorganization or liquidation, involving the Issuer or any of its subsidiaries; (c) a sale or transfer of a material amount of the assets of the Issuer or any of its subsidiaries; (d) any change in the present Board of Directors or management of the Issuer, including any plans or proposals to change the number or term of directors or to fill any existing vacancies on the board; (e) any material change in the Issuer’s capitalization or dividend policy of the Issuer; (f) any other material change in the Issuer’s business or corporate structure; (g) any change in the Issuer’s charter or bylaws or other instrument corresponding thereto or other action which may impede the acquisition of control of the Issuer by any person; (h) causing a class of the Issuer’s securities to be deregistered or delisted from a national securities exchange or to cease to be authorized to be quoted in an inter-dealer quotation system of a registered national securities association; (i) a class of equity securities of the Issuer becoming eligible for termination of registration pursuant to Section 12(g)(4) of the Act; or (j) any action similar to any of those enumerated above.

Item 5. Interest in Securities of the Issuer

(a) — (b) The following disclosure is based upon 29,220,176 outstanding Shares, as set forth in the Issuer’s Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (the “SEC”) on November 10, 2021.

As of the date of this filing, OPI VI holds 3,656,061 Shares and 145,251 Shares issuable upon the exercise of the Warrants, constituting approximately 12.9% of the issued and outstanding Shares. GP VI is the general partner of OPI VI pursuant to the terms of the limited partnership agreement of OPI VI, and OrbiMed Advisors is the managing member of GP VI, pursuant to the terms of the limited liability company agreement of GP VI. As a result, OrbiMed Advisors and GP VI share power to direct the vote and disposition of the Shares held by OPI VI and may be deemed directly or indirectly, including by reason of their mutual affiliation, to be the beneficial owners of the Shares held by OPI VI. OrbiMed Advisors exercises this investment and voting power through a management committee comprised of Carl L. Gordon, Sven H. Borho, and W. Carter Neild, each of whom disclaims beneficial ownership of the Shares held by OPI VI.

As of the date of this filing, Genesis Master Fund holds 425,531 Shares constituting approximately 1.5% of the issued and outstanding Shares. OrbiMed Genesis is the general partner of Genesis Master Fund, pursuant to the terms of the limited partnership agreement of Genesis Master Fund, and OrbiMed Advisors is the managing member of OrbiMed Genesis, pursuant to the terms of the limited liability company agreement of OrbiMed Genesis. As a result, OrbiMed Advisors and OrbiMed Genesis share power to direct the vote and disposition of the Shares held by Genesis Master Fund and may be deemed, directly or indirectly, including by reason of their mutual affiliation, to be the beneficial owners of the Shares held by Genesis Master Fund. OrbiMed Advisors exercises this investment and voting power through a management committee comprised of Carl L. Gordon, Sven H. Borho, and W. Carter Neild, each of whom disclaims beneficial ownership of the Shares held by Genesis Master Fund.

In addition, OrbiMed Advisors and GP VI, pursuant to their authority under the limited partnership agreements of OPI VI, caused OPI VI to enter into the Registration Rights Agreement referred to in Item 6 below.

(c)

Purchaser	Date of Transaction	Transaction	Number of Shares	Price Per Share
OPI VI	September 17, 2021	Purchase	585,106	\$9.40
Genesis Master Fund	September 17, 2021	Purchase	425,531	\$9.40

(d) Not applicable.

(e) Not applicable.

Item 6. Contracts, Arrangements, Understandings or Relationship with Respect to Securities of the Issuer

In addition to the relationships between the Reporting Persons described in Items 2 and 5 above, GP VI is the general partner of OPI VI, pursuant to the terms of the limited partnership agreement of OPI VI. Pursuant to this agreement and relationship, GP VI has discretionary investment management authority with respect to the assets of OPI VI. Such authority includes the power to vote and otherwise dispose of securities held by OPI VI. The number of outstanding Shares of the Issuer attributable to OPI VI is 3,656,061 Shares and 145,251 Shares issuable upon the exercise of the Warrants. GP VI, pursuant to its authority under the limited partnership agreement of OPI VI, may be considered to hold indirectly 3,801,312 Shares.

OrbiMed Genesis is the general partner of Genesis Master Fund, pursuant to the terms of the limited partnership agreement of Genesis Master Fund. Pursuant to this agreement and relationship, OrbiMed Genesis has discretionary investment management authority with respect to the assets of Genesis Master Fund. Such authority includes the power to vote and otherwise dispose of securities held by Genesis Master Fund. The number of outstanding Shares of the Issuer attributable to Genesis Master Fund is 425,531. OrbiMed Genesis, pursuant to its authority under the limited partnership agreement of Genesis, may be considered to hold indirectly 425,531 Shares.

OrbiMed Advisors is the managing member of GP VI and OrbiMed Genesis, pursuant to the terms of the limited liability company agreements of GP VI and OrbiMed Genesis. Pursuant to these agreements and relationships, OrbiMed Advisors and GP VI have discretionary investment management authority with respect to the assets of OPI VI. OrbiMed Advisors and OrbiMed Genesis have discretionary investment management authority with respect to the assets of Genesis Master Fund. Such authority includes the power of GP VI to vote and otherwise dispose of securities held by OPI VI and the power of OrbiMed Genesis to vote and otherwise dispose of the securities held by Genesis Master Fund. The number of outstanding Shares attributable to OPI VI is 3,656,061 Shares and 145,251 Shares issuable upon the exercise of the Warrants and the number of Shares attributed to Genesis Master Fund is 425,531 Shares. OrbiMed Advisors, pursuant to its authority under the terms of the limited liability company agreements of GP VI and OrbiMed Genesis, may also be considered to hold indirectly 4,226,843 Shares.

Registration Rights Agreement.

OPI VI and certain other stockholders of the Issuer entered into a Registration Rights Agreement with the Issuer, a summary of which is set forth in Item 6 of the Amendment No. 2.

Other than as described in this Amendment No. 5, to the best of the Reporting Persons' knowledge, there are no other contracts, arrangements, understandings or relationships (legal or otherwise) among the persons named in Item 2 and between such persons and any person with respect to any securities of the Issuer.

Item 7. Materials to Be Filed as Exhibits

Exhibit	Description
1.	Joint Filing Agreement among OrbiMed Advisors LLC, OrbiMed Capital GP VI LLC, and OrbiMed Genesis GP LLC.
2.	Registration Rights Agreement by and among the Issuer and the Purchasers, dated January 15, 2019 (incorporated by reference to Exhibit 10.2 to the Issuer's Current Report on Form 8-K (SEC 001-37449), filed with the SEC on January 16, 2019).

SIGNATURE

After reasonable inquiry and to the best of each of the undersigned's knowledge and belief, each of the undersigned certifies that the information set forth in this statement is true, complete and correct.

Dated: November 12, 2021

OrbiMed Advisors LLC

By: /s/ Carl L. Gordon
Name: Carl L. Gordon
Title: Member

OrbiMed Capital GP VI LLC

By: OrbiMed Advisors LLC
its Managing Member

By: /s/ Carl L. Gordon
Name: Carl L. Gordon
Title: Member of OrbiMed Advisors LLC

OrbiMed Genesis GP LLC

By: OrbiMed advisors LLC, its managing member

By: /s/ Carl L. Gordon
Name: Carl L. Gordon
Title: Member of OrbiMed Advisors LLC

Schedule I

The name and present principal occupation of each of the executive officers and directors of OrbiMed Advisors LLC are set forth below. Unless otherwise noted, each of these persons are United States citizens and have as their business address 601 Lexington Avenue, 54th Floor, New York, NY 10022.

<u>Name</u>	<u>Position with Reporting Person</u>	<u>Principal Occupation</u>
Carl L. Gordon	Member	Member OrbiMed Advisors LLC
Sven H. Borho German and Swedish Citizen	Member	Member OrbiMed Advisors LLC
Jonathan T. Silverstein	Member	Member OrbiMed Advisors LLC
W. Carter Neild	Member	Member OrbiMed Advisors LLC
Geoffrey C. Hsu	Member	Member OrbiMed Advisors LLC
C. Scotland Stevens	Member	Member OrbiMed Advisors LLC
David P. Bonita	Member	Member OrbiMed Advisors LLC
Trey Block	Chief Financial Officer	Chief Financial Officer OrbiMed Advisors LLC

Schedule II

The business and operations of OrbiMed Capital GP VI LLC are managed by the executive officers and directors of its managing member, OrbiMed Advisors LLC, set forth on Schedule I attached hereto.

SCHEDULE III

The business and operations of OrbiMed Genesis GP LLC are managed by the executive officers and directors of its managing member, OrbiMed Advisors LLC, set forth in Schedule I attached hereto.

EXHIBIT INDEX

Exhibit	Description
1.	Joint Filing Agreement among OrbiMed Advisors LLC, OrbiMed Capital GP VI LLC, and OrbiMed Genesis GP LLC.
2.	Registration Rights Agreement by and among the Issuer and the Purchasers, dated January 15, 2019 (incorporated by reference to Exhibit 10.2 to the Issuer's Current Report on Form 8-K (SEC 001-37449), filed with the SEC on January 16, 2019).

JOINT FILING AGREEMENT

The undersigned hereby agree that this Amendment No. 5 to the Statement on this Schedule 13D, dated November 12, 2021 (the “Schedule 13D”), with respect to the Shares of Alpine Immune Sciences, Inc. is filed, and all amendments thereto will be filed, on behalf of each of us pursuant to and in accordance with the provisions of Rule 13d-1(k) under the Securities and Exchange Act of 1934, as amended, and that this Agreement shall be included as an Exhibit to this Schedule 13D. Each of the undersigned agrees to be responsible for the timely filing of the Schedule 13D, and for the completeness and accuracy of the information concerning itself contained therein. This Agreement may be executed in any number of counterparts, all of which taken together shall constitute one and the same instrument.

IN WITNESS WHEREOF, the undersigned have executed this Agreement as of the 12th day of November 2021.

OrbiMed Advisors LLC

By: /s/ Carl L. Gordon
 Name: Carl L. Gordon
 Title: Member

OrbiMed Capital GP VI LLC

By: OrbiMed Advisors LLC
 its Managing Member

By: /s/ Carl L. Gordon
 Name: Carl L. Gordon
 Title: Member of OrbiMed Advisors LLC

OrbiMed Genesis GP LLC

By: OrbiMed advisors LLC, its managing member

By: /s/ Carl L. Gordon
 Name: Carl L. Gordon
 Title: Member of OrbiMed Advisors LLC
