



Alpine Immune Sciences, Inc.

7,709,416 Shares of Common Stock

This prospectus relates to the disposition, from time to time, by the selling stockholders identified in this prospectus under the caption "Selling Stockholders" on page 8 of up to 7,709,416 shares of our common stock, including shares issuable upon the exercise of warrants to purchase our common stock and shares issuable upon the exercise of prefunded warrants to purchase our common stock.

The selling stockholders or their permitted transferees or other successors-in-interest may, but are not required to, sell the shares of our common stock offered by this prospectus from time to time in a number of different ways and at varying prices as determined by the prevailing market price for shares or in negotiated transactions. See "Plan of Distribution" on page 12 for a description of how the selling stockholders may dispose of the shares covered by this prospectus. We do not know when or in what amount the selling stockholders may offer the shares for sale.

We are not selling any shares of our common stock under this prospectus and will not receive any proceeds from the sale of shares of common stock by the selling stockholders. We will receive proceeds from the cash exercise of the warrants which, if exercised for cash with respect to all of the 1,779,096 shares of common stock underlying such warrants at the exercise price per share of \$12.74, would result in gross proceeds to us of approximately \$22.7 million. We also will receive proceeds from the cash exercise of the prefunded warrants which, if exercised for cash with respect to all of the 790,710 shares of common stock underlying such warrants at the exercise price per share of \$0.001, would result in gross proceeds to us of approximately \$791. We have agreed to pay certain expenses related to the registration of the offer and sale of the shares of common stock pursuant to the registration statement of which this prospectus forms a part. The selling stockholders will bear all commissions and discounts, if any, attributable to the sale of the shares.

Our common stock is listed on The Nasdaq Global Market under the symbol "ALPN." On May 18, 2021, the last reported closing sale price of our common stock on The Nasdaq Global Market was \$13.73 per share.

Investing in our common stock involves a high degree of risk. You should review carefully the risks and uncertainties described under the heading "Risk Factors" starting on page 4 of this prospectus, and under similar headings in the documents that are incorporated by reference into this prospectus.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

The date of this prospectus is May 18, 2021.

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This prospectus is part of a resale registration statement that we filed with the Securities and Exchange Commission, or the SEC, using a “shelf” registration process. Under this shelf registration process, the selling stockholders may, from time to time, offer and sell the common stock described in this prospectus.

You should rely only on the information contained in, or incorporated by reference into, this prospectus or contained in any free writing prospectus prepared by or on behalf of us or to which we have referred you. Neither we nor the selling stockholders have authorized anyone to provide any information or to make any representations other than those contained in, or incorporated by reference into, this prospectus or in any free writing prospectuses prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus is an offer to sell only the securities offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. The information contained in, or incorporated by reference into, this prospectus is accurate only as of its date regardless of the time of delivery of this prospectus or of any sale of securities. Our business, financial condition, operating results and prospects may have changed since that date.

You should also read and consider the information in the documents to which we have referred you under the captions “Where You Can Find More Information” and “Information Incorporated by Reference” in this prospectus.

For investors outside the United States, neither we nor the selling stockholders have done anything that would permit this offering or possession or distribution of this prospectus in any jurisdiction where action for that purpose is required, other than in the United States. Persons who come into possession of this prospectus and any free writing prospectus related to this offering in jurisdictions outside the United States are required to inform themselves about and to observe any restrictions as to this offering and the distribution of this prospectus and any such free writing prospectus applicable to that jurisdiction.

PROSPECTUS SUMMARY

The following summary is qualified in its entirety by, and should be read together with, the more detailed information and financial statements and related notes thereto incorporated by reference into this prospectus. Before you decide to invest in our common stock, you should read the entire prospectus carefully, including the risk factors and the financial statements and related notes incorporated by reference into this prospectus. Unless the context requires otherwise, in this prospectus the terms “Alpine,” the “Company,” “we,” “us” and “our” refer to Alpine Immune Sciences, Inc., together with its subsidiaries, taken as a whole. This prospectus includes trademarks, service marks and trade names owned by us or other companies. All trademarks, service marks and trade names included in this prospectus are the property of their respective owners.

Company Overview

We are a clinical-stage biopharmaceutical company dedicated to discovering and developing innovative, protein-based immunotherapies to treat cancer and autoimmune and inflammatory diseases. Our approach includes a proprietary scientific platform that converts native immune system proteins into differentiated, multi-targeted therapeutics. We believe our strategies are capable of meaningfully modulating the human immune system and significantly improving outcomes in patients with serious diseases.

ALPN-101 is a dual inducible T cell costimulatory, or ICOS, and cluster of differentiation 28, or CD28, antagonist intended for the treatment of autoimmune and inflammatory diseases. Preclinical studies have demonstrated efficacy in models of systemic lupus erythematosus, or SLE, Sjögren’s syndrome, or SjS, arthritis, inflammatory bowel disease, multiple sclerosis, type 1 diabetes, uveitis, and graft versus host disease, or GVHD. In June 2020, we entered into an Option and License agreement with AbbVie Ireland Unlimited Company, or AbbVie, which grants to AbbVie an exclusive option to take an exclusive license to ALPN-101. Under the terms of the agreement, we received an upfront payment of \$60 million, and are eligible to receive up to an aggregate of \$805 million for AbbVie’s exercise of the option and success-based development, regulatory and commercial milestones. In addition, we are eligible to receive tiered royalties on net sales of ALPN-101. We have successfully received U.S. FDA IND clearance, and anticipate that a study will commence enrollment in mid-2021.

ALPN-303 is a dual B cell cytokine antagonist being developed for B cell-mediated autoimmune/inflammatory diseases. Engineered using our proprietary directed evolution platform, ALPN-303 is a potent inhibitor of the pleiotropic B cell cytokines B cell activating factor, or BAFF, and a proliferation inducing ligand, or APRIL, which may play key roles in certain autoimmune/inflammatory disease through their regulation of B cell development, differentiation, and survival. We are targeting completion of activities to support initiation of a Phase 1 healthy volunteer study with ALPN-303 in the fourth quarter of 2021.

Our lead oncology program is ALPN-202, a conditional CD28 costimulator and dual checkpoint inhibitor intended for the treatment of cancer. Preclinical *in vivo* data have demonstrated monotherapy efficacy in tumor models superior to approved therapies. In addition, ALPN-202 has a unique immuno-modulatory profile and has demonstrated evidence of anti-tumor immunity in preclinical models. Based on ALPN-202’s efficacy in preclinical models and favorable nonclinical safety and development profile, we initiated NEON-1, a Phase 1 dose escalation and expansion study in patients with advanced malignancies, in 2020 and intend to continue enrolling patients throughout 2021. We also intend to initiate NEON-2, a Phase 1 combination study of ALPN-202 and a PD-1 inhibitor later this year.

Our scientific platform has also generated immune modulatory proteins with the potential of improving engineered cellular therapies, or ECT, such as chimeric antigen receptor T cells, or CAR-T, T cell receptor-engineered T cells, or TCR-T, and tumor infiltrating lymphocytes, or TILs. In May 2019, we signed a collaboration and license agreement with Adaptimmune Therapeutics plc, or Adaptimmune, to develop next-generation SPEAR™ T cell products which incorporate our secreted and transmembrane

immunomodulatory protein (termed SIP™ and TIP™) technology. We intend to continue to leverage our existing pipeline and platform to actively explore and evaluate potential value-creating partnering opportunities.

Corporate Information

In July 2017, Alpine Immune Sciences, Inc. completed its business combination with Nivalis Therapeutics, Inc., a publicly held company. In connection with the merger, Nivalis Therapeutics, Inc. changed its name to Alpine Immune Sciences, Inc. Nivalis Therapeutics, Inc. was incorporated in Delaware in March 2007. Alpine Immune Sciences, Inc. (prior to its business combination with Nivalis Therapeutics, Inc.) was incorporated in Delaware in December 2014.

Our principal executive office is located at 188 East Blaine Street, Suite 200, Seattle, WA, 98102. Our telephone number is (206) 788-4545. Our website is www.alpineimmunesciences.com. Information contained in, or that can be accessed through, our website is not a part of, and is not incorporated into, this prospectus.

The Offering

The selling stockholders named in this prospectus may offer and sell up to 7,709,416 shares of our common stock. Our common stock is listed on The Nasdaq Global Market under the symbol “ALPN.” We will not receive any of the proceeds from sales by the selling stockholders of any of the shares of common stock covered by this prospectus. We will receive proceeds from any cash exercise of warrants and prefunded warrants to purchase the shares included in the shares that are being offered by the selling stockholders hereunder. We intend to use any such proceeds to fund the development of our preclinical and clinical pipeline, including ALPN-101, in systemic lupus erythematosus, ALPN-202, in patients with advanced malignancies, ALPN-303 in B cell-mediated inflammatory diseases, as well as for general corporate purposes. See “Use of Proceeds” on page 7.

Throughout this prospectus, when we refer to the shares of our common stock, the offer and sale of which are being registered on behalf of the selling stockholders, we are referring to the shares of common stock that have been issued to or are issuable upon the exercise of warrants and prefunded warrants to the stockholders listed in “Selling Stockholders” on page 8, pursuant to the securities purchase agreement described below. When we refer to the selling stockholders in this prospectus, we are referring to the investors in our July 2020 private placement and, as applicable, any donees, pledgees, transferees or other successors-in-interest selling shares received after the date of this prospectus from the investors in our July 2020 private placement as a gift, pledge, or other non-sale related transfer.

July 2020 Private Placement

On July 24, 2020, we entered into a securities purchase agreement for a private placement with a select group of institutional investors, including Omega Funds, Avidity Partners, EcoR1 Capital, LLC, Invus Public Equities, L.P., and Samsara BioCapital and other accredited investors, which we collectively refer to as the Purchasers. Pursuant to the securities purchase agreement, the Purchasers purchased (a) 5,139,610 units, or Common Units, representing (1) 5,139,610 shares of our common stock, par value \$0.001 per share, or the Shares, and (2) warrants to purchase up to an aggregate of 1,541,883 shares of common stock at an exercise price of \$12.74 per share, subject to adjustments as provided under the terms of the warrants and (b) 790,710 units, or Prefunded Units, representing (1) prefunded warrants to purchase up to an aggregate of 790,710 shares of common stock at an exercise price of \$0.001 per share, subject to adjustments as provided under the terms of the prefunded warrants, and (2) warrants to purchase up to an aggregate of 237,213 shares of

common stock at an exercise price of \$12.74 per share, subject to adjustments as provided under the terms of the warrants. The Common Units and the Prefunded Units are collectively referred to as the Units. The purchase price for each Unit was \$10.1175, for an aggregate purchase price of approximately \$60.0 million. The closing of the purchase and sale of the Units occurred on July 28, 2020.

The warrants are immediately exercisable and have a 3.5 year term. The prefunded warrants are immediately exercisable.

We also entered into a registration rights agreement with the Purchasers requiring us to register the resale of the Shares and the shares issuable upon exercise of the warrants and prefunded warrants.

RISK FACTORS

An investment in our securities has a high degree of risk. Before you invest you should carefully consider the risks and uncertainties described under “Part I. Item 1A — Risk Factors” in our Annual Report on [Form 10-K](#), filed with the SEC on March 18, 2021, and “Part II. Item 1A — Risk Factors” in our Quarterly Report on [Form 10-Q](#), filed with the SEC on May 13, 2021, which are incorporated by reference in this prospectus, together with all of the other information contained in this prospectus and the documents incorporated by reference herein. If any of these risks actually occur, our business, operating results and financial condition could be materially and adversely impacted, the market price of our common stock could decline and you could lose all or part of your investment. Additional risks and uncertainties not presently known or which we consider immaterial as of the date hereof may also have an adverse effect on our business.

CAUTIONARY NOTES REGARDING FORWARD-LOOKING STATEMENTS

This prospectus and the information incorporated by reference herein may contain “forward-looking statements” within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, which are subject to the “safe harbor” created by those sections. Forward-looking statements are identified by words such as “believe,” “anticipate,” “expect,” “intend,” “plan,” “will,” “may,” “seek,” “estimate,” “continue,” “could,” “would,” “project,” and other similar expressions, or the negative or plural of these words or expressions. You should read these statements carefully because they discuss future expectations, contain projections of future results of operations or financial condition, or state other “forward-looking” information. These statements relate to our future plans, objectives, expectations, intentions and financial performance and the assumptions that underlie these statements. These forward-looking statements include, but are not limited to:

- our ability to identify, develop and commercialize additional products or product candidates;
- our estimates regarding our expenses, revenues, anticipated capital requirements and our needs for additional financing;
- our ability to obtain funding for our operations;
- the implementation of our business model and strategic plans for our business and technology;
- the timing of the commencement, progress and receipt of data from any of our preclinical and clinical trials;
- the expected results of any preclinical or clinical trial and the impact on the likelihood or timing of any regulatory approval;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our technology and product candidates;
- the anticipated impact of the COVID-19 pandemic on our business, research and clinical development plans and timeliness and results of operations;
- the timing or likelihood of regulatory filings and approvals;
- the therapeutic benefits, effectiveness and safety of our product candidates;
- the rate and degree of market acceptance and clinical utility of any future products;
- our ability to maintain and establish collaborations;
- our ability to achieve milestones in our current and any future collaborations;
- our expectations regarding market risk, including interest rate changes;
- our expectations regarding the sufficiency of our cash and cash equivalents to fund operations for at least the next 12 months;

- our expected use of the net proceeds, if any, of any cash exercise of the warrants and prefunded warrants;
- developments relating to our competitors and our industry; and
- our expectations regarding licensing, acquisitions and strategic operations.

All forward-looking statements are based on information available to us on the date of this prospectus and we will not update any of the forward-looking statements after the date of this prospectus, except as required by law. Our actual results could differ materially from those discussed in this prospectus. The forward-looking statements contained in this prospectus, and other written and oral forward-looking statements made by us from time to time, are subject to certain risks and uncertainties that could cause actual results to differ materially from those anticipated in the forward-looking statements. Factors that might cause such a difference include, but are not limited to, those discussed under "Part I. Item 1A — Risk Factors" in our Annual Report on [Form 10-K](#), filed with the SEC on March 18, 2021, and "Part II. Item 1A — Risk Factors" in our Quarterly Report on [Form 10-Q](#), filed with the SEC on May 13, 2021, which are incorporated by reference in this prospectus. Forward-looking statements are based on our management's beliefs and assumptions and on information currently available to our management. These statements, like all statements in this prospectus, speak only as of their date, and we undertake no obligation to update or revise any forward-looking statements in light of future developments, except as required by law.

In addition, statements that "we believe" and similar statements reflect our beliefs and opinions on the relevant subject. These statements are based upon information available to us as of the date of this prospectus, and while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. These statements are inherently uncertain and investors are cautioned not to unduly rely upon these statements.

USE OF PROCEEDS

We will not receive any proceeds from the sale of shares of common stock by the selling stockholders.

We will receive proceeds from the cash exercise of the warrants which, if exercised for cash with respect to all of the 1,779,096 shares of common stock underlying such warrants at the exercise price per share of \$12.74, would result in gross proceeds to us of approximately \$22.7 million. We also will receive proceeds from the cash exercise of the prefunded warrants which, if exercised for cash with respect to all of the 790,710 shares of common stock underlying such prefunded warrants at the exercise price per share of \$0.001, would result in gross proceeds to us of approximately \$791. There can be no assurance that any of the warrants or prefunded warrants will be exercised by the selling stockholders or that they will exercise the warrants or prefunded warrants for cash instead of using the cashless exercise feature.

We intend to use the net proceeds, if any, from the cash exercise of the warrants and prefunded warrants to fund the development of our preclinical and clinical pipeline, including ALPN-101, in systemic lupus erythematosus, ALPN-202, in patients with advanced malignancies, ALPN-303 in B cell-mediated inflammatory diseases, as well as for general corporate purposes. The amounts and timing of our actual expenditures for each purpose may vary significantly depending upon numerous factors, including the status of our product development and preclinical and clinical trial efforts, regulatory approvals, competition, marketing and sales activities and the market acceptance of any products introduced by us. We reserve the right to change the use of proceeds as a result of certain contingencies such as competitive developments, opportunities to acquire technologies or products and other factors. Pending application of the proceeds, if any, from the cash exercise of the warrants and the prefunded warrants, we intend to invest the net proceeds in short-term, investment-grade, interest-bearing instruments, certificates of deposit or direct or guaranteed obligations of the U.S. government.

SELLING STOCKHOLDERS

We have included in this prospectus and related registration statement 7,709,416 shares of our common stock (including common stock issuable upon exercise of the warrants and prefunded warrants) issued in our July 2020 private placement to the selling stockholders. The term “selling stockholder” includes the stockholders listed below and their transferees, pledges, donees or other successors in interest selling Shares received after the date of this prospectus from a selling stockholder as a gift, pledge, partnership distribution or other non-sale related transfer. Information concerning the selling stockholders may change after the date of this prospectus and changed information will be presented in a supplement to this prospectus if and when required.

The table below sets forth certain information with respect to each selling stockholder, including (i) the name and address of each selling stockholder; (ii) the number of shares of our common stock beneficially owned by each selling stockholder prior to this offering; (iii) the maximum number of shares being offered by each selling stockholder pursuant to this prospectus; and (iv) each selling stockholder’s beneficial ownership after completion of this offering, assuming that all of the shares covered hereby (but no other shares, if any, held by the selling stockholders) are sold.

The table is based on information supplied to us by the selling stockholders, with beneficial ownership and percentage ownership determined in accordance with the rules and regulations of the SEC, and includes information with respect to voting or investment power with respect to shares of stock. This information does not necessarily indicate beneficial ownership for any other purpose.

The percentage of each selling stockholder’s ownership is based on 23,784,850 shares of common stock outstanding as of July 31, 2020. In computing the number of shares beneficially owned by a selling stockholder and the percentage ownership of that selling stockholder before this offering, shares of common stock underlying the warrants and prefunded warrants held by that selling stockholder, are deemed outstanding, as well as any other derivative securities that are exercisable as of July 31, 2020, or exercisable within 60 days thereafter. Such shares, however, are not deemed outstanding for the purposes of computing the percentage ownership of any other person. The percentage of beneficial ownership after this offering is based on shares outstanding on July 31, 2020, which includes the shares of our common stock registered for sale in this offering. The ownership information for the selling stockholders prior to this offering does not give effect to any acquisitions or dispositions of our common stock made after July 31, 2020.

The registration of the sale of shares of common stock held by and issuable to the selling stockholders upon exercise of the warrants and prefunded warrants does not mean that the selling stockholders will sell or otherwise dispose of all or any of those securities. The selling stockholders may sell or otherwise dispose of all, a portion or none of such shares from time to time. We do not know the number of shares, if any, that will be offered for sale or other disposition by any of the selling stockholders under this prospectus. Furthermore, the selling stockholders may have sold, transferred or disposed of the shares of common stock covered hereby in transactions exempt from the registration requirements of the Securities Act since the date on which we filed this prospectus.

None of the selling stockholders has, or within the past three years has had, any position, office or other material relationship with us or any of our predecessors or affiliates. None of the selling stockholders is a broker-dealer or an affiliate of a broker-dealer, except as noted below.

Selling Stockholder(1)	Beneficial Ownership Before This Offering		Shares Offered Hereby(3)	Shares Issuable upon Exercise of Warrants	Shares Issuable upon Exercise of Prefunded Warrants	Beneficial Ownership After This Offering	
	Number of Shares Owned	Percentage of Outstanding Shares(2)				Number of Shares Owned	Percentage of Outstanding Shares
Omega Fund VI, L.P.(4)	1,670,370	6.9 %	1,284,900	385,470	—	—	—%
Baker Brothers Life Sciences, L.P.(5)	960,856	3.9 %	—	221,736	739,120	—	—%
667, L.P.(5)	67,067	*	—	15,477	51,590	—	—%
Avidity Capital Fund II LP(6)	109,213	*	84,010	25,203	—	—	—%
Avidity Master Fund LP(6)	854,477	3.6 %	657,290	197,187	—	—	—%
EcoR1 Capital Fund, L.P.(7)	149,461	*	114,970	34,491	—	—	—%
EcoR1 Capital Fund Qualified, L.P.(7)	814,216	3.4 %	626,320	187,896	—	—	—%
Farallon Capital F5 Master I, L.P.(8)	62,153	*	47,810	14,343	—	—	—%
Farallon Capital (AM) Investors, L.P.(8)	15,132	*	11,640	3,492	—	—	—%
Farallon Capital Institutional Partners II, L.P. (8)	36,530	*	28,100	8,430	—	—	—%
Farallon Capital Institutional Partners III, L.P.(8)	17,446	*	13,420	4,026	—	—	—%
Four Crossings Institutional Partners V, L.P. (8)	26,884	*	20,680	6,204	—	—	—%
Farallon Capital Institutional Partners, L.P. (8)	180,791	*	139,070	41,721	—	—	—%
Farallon Capital Offshore Investors II, L.P. (8)	508,430	2.1 %	391,100	117,330	—	—	—%
Farallon Capital Partners, L.P.(8)	116,311	*	89,470	26,841	—	—	—%
Invus Public Equities, L.P.(9)	770,939	3.2 %	593,030	177,909	—	—	—%
Samsara BioCapital, L.P.(10)	642,447	2.7 %	494,190	148,257	—	—	—%
DAFNA LifeScience, L.P.(11)	142,623	*	109,710	32,913	—	—	—%
DAFNA LifeScience Select, L.P.(11)	50,115	*	38,550	11,565	—	—	—%
Sphera Biotech Master Fund, L.P.(12)	192,738	*	148,260	44,478	—	—	—%
CVI Investments, Inc.(13)	128,492	*	98,840	29,652	—	—	—%
Monashee Solitario Fund LP(14)	37,258	*	28,660	8,598	—	—	—%
Monashee Pure Alpha SPV I LP(14)	28,275	*	21,750	6,525	—	—	—%
BEMAP Master Fund LTD(14)	62,959	*	48,430	14,529	—	—	—%
Driehaus Life Sciences Master Fund, L.P. (15)	64,233	*	49,410	14,823	—	—	—%
Total:	<u>7,709,416</u>	<u>29.3 %</u>	<u>5,139,610</u>	<u>1,779,096</u>	<u>790,710</u>	<u>—</u>	<u>—%</u>

(*) Less than one percent.

- (1) This table and the information in the notes below are based upon information supplied by the selling stockholders and are based on shares of common stock outstanding as of July 31, 2020. Warrants exercisable within 60 days of July 31, 2020 are deemed outstanding for the purposes of computing the percentage of shares owned by that person, but are not deemed outstanding for purposes of computing the percentage of shares owned by any other person.
- (2) The warrants and prefunded warrants held by the selling stockholders are subject in certain cases to beneficial ownership limitations such that the warrants and prefunded warrants may not be exercised if it would result in the holder exceeding the beneficial ownership limitation (the "Beneficial Ownership Limitation"). The Beneficial Ownership Limitation is 4.99% in the aggregate for the warrants held by the Baker Funds (as defined below), the EcoR1 Funds (as defined

- below), the Farallon Funds (as defined below), the DAFNA Funds (as defined below), CVI (as defined below) and the Monashee Funds (as defined below). The Beneficial Ownership Limitation is 9.99% in the aggregate for the prefunded warrants held by the Baker Funds.
- (3) Does not include shares issuable upon the exercise of the warrants or prefunded warrants.
- (4) Consists of 1,284,900 shares of common stock and warrants to purchase up to an aggregate of 385,470 shares of common stock held directly by Omega Fund VI, L.P. (“Omega Fund”). Omega Fund VI GP Manager, Ltd. (“Omega Ltd.”) serves as the general partner of Omega Fund VI GP, L.P. (“Omega GP”), which serves as the general partner of Omega Fund; and each of Omega Ltd and Omega GP may be deemed to own beneficially the shares held by Omega Fund. Claudio Nessi, Otello Stampacchia and Anne-Mari Paster are the directors of Omega Ltd and may be deemed to beneficially own the shares held directly by Omega Fund. The address of the selling stockholder is 888 Boylston Street, Suite 1111, Boston, MA 02199.
- (5) Consists of (i) prefunded warrants to purchase up to an aggregate of 739,120 shares of common stock and warrants to purchase up to an aggregate of 221,736 shares of common stock held directly by Baker Brothers Life Sciences, L.P. (“BBLs”) and (ii) prefunded warrants to purchase up to an aggregate of 51,590 shares of common stock and warrants to purchase up to an aggregate of 15,477 shares of common stock held directly by 667, L.P. (“667” and together with BBLs, the “Baker Funds”). Baker Bros. Advisors LP is the investment advisor to the Baker Funds. Baker Bros. Advisors (GP) LLC is the sole general partner of Baker Bros. Advisors LP. Julian C. Baker and Felix J. Baker are managing members of Baker Bros. Advisors (GP) LLC and as a result may be deemed to have voting and dispositive power over the securities held directly by the Baker Funds. The address of the selling stockholders is 860 Washington Street, 3rd Floor, New York, NY 10014.
- (6) Consists of (i) 84,010 shares of common stock and warrants to purchase up to an aggregate of 25,203 shares of common stock held directly by Avidity Capital Fund II LP (“Avidity Capital”) and (ii) 657,290 shares of common stock and warrants to purchase up to an aggregate of 197,187 shares of common stock held directly by Avidity Master Fund LP (“Avidity Master” and together with Avidity Capital, the “Avidity Funds”). David Roy Witzke and Michael David Gregory directly or indirectly control the Avidity Funds and as a result may be deemed to have voting and dispositive power over the securities held directly by the Avidity Funds. The address of the selling stockholders is 2828 N. Harwood St., Suite 1220, Dallas, TX 75201.
- (7) Consists of (i) 114,970 shares of common stock and warrants to purchase up to an aggregate of 34,491 shares of common stock held directly by EcoR1 Capital Fund, L.P. (“EcoR1 Capital”) and (ii) 626,320 shares of common stock and warrants to purchase up to an aggregate of 187,896 shares of common stock held directly by EcoR1 Capital Fund Qualified, L.P. (“EcoR1 Qualified” and together with EcoR1 Capital, the “EcoR1 Funds”). Oleg Nodelman directly or indirectly controls the EcoR1 Funds and as a result may be deemed to have voting and dispositive power over the securities held directly by the EcoR1 Funds. The address of the selling stockholders is 357 Tehama Street, #3, San Francisco, CA 94103.
- (8) Consists of (i) 47,810 shares of common stock and warrants to purchase up to an aggregate of 14,343 shares of common stock held directly by Farallon Capital F5 Master I, L.P. (“FCF5”), (ii) 11,640 shares of common stock and warrants to purchase up to an aggregate of 3,492 shares of common stock held directly by Farallon Capital (AM) Investors, L.P. (“FCAM”), (iii) 28,100 shares of common stock and warrants to purchase up to an aggregate of 8,430 shares of common stock held directly by Farallon Capital Institutional Partners II, L.P. (FCIP II”), (iv) 13,420 shares of common stock and warrants to purchase up to an aggregate of 4,026 shares of common stock held directly by Farallon Capital Institutional Partners III, L.P. (“FCIP III”), (v) 20,680 shares of common stock and warrants to purchase up to an aggregate of 6,204 shares of common stock held directly by Four Crossings Institutional Partners V, L.P. (“FCIP V”), (vi) 139,070 shares of common stock and warrants to purchase up to an aggregate of 41,721 shares of common stock held directly by Farallon Capital Institutional Partners, L.P. (“FCIP”), (vii) 391,100 shares of common stock and warrants to purchase up to an aggregate of 117,330 shares of common stock held directly by Farallon Capital Offshore Investors II, L.P. (“FCOI”) and (viii) 89,470 shares of common stock and warrants to purchase up to an aggregate of 26,841 shares of common stock held directly by Farallon Capital Partners, L.P. (“FCP” and together with FCF5, FCAM, FCIP II, FCIP III, FCIP V, FCIP and FCOI, the “Farallon Funds”). Philip D. Dreyfuss, Michael B. Fisch, Richard B. Fried, David T. Kim, Michael G. Linn, Rajiv A. Patel, Thomas G. Roberts, Jr., William Seybold, Andrew J.M. Spokes, John R. Warren and Mark C. Wehrly directly or indirectly control the Farallon Funds and as a result may be deemed to have voting and dispositive power over the securities held directly by the Farallon Funds. The address of the selling stockholders is c/o Farallon Capital Management, L.L.C., One Maritime Plaza, Suite 2100, San Francisco, CA 94111.

- (9) Consists of 593,030 shares of common stock and warrants to purchase up to an aggregate of 177,909 shares of common stock held directly by Invus Public Equities, L.P. The address of the selling stockholder is 750 Lexington Avenue, 30th Floor, New York, NY 10022.
- (10) Consists of 494,190 shares of common stock and warrants to purchase up to an aggregate of 148,257 shares of common stock held directly by Samsara BioCapital, L.P. The address of the selling stockholder is c/o Samsara BioCapital, 628 Middlefield Road, Palo Alto, CA 94301.
- (11) Consists of (i) 109,710 shares of common stock and warrants to purchase up to an aggregate of 32,913 shares of common stock held directly by DAFNA LifeScience, L.P. ("DAFNA") and (ii) 38,550 shares of common stock and warrants to purchase up to an aggregate of 11,565 shares of common stock held directly by DAFNA LifeScience Select, L.P. ("DAFNA Select" and together with DAFNA, the "DAFNA Funds"). Fariba Ghodsian and Nathan Fischel directly or indirectly control the DAFNA Funds and as a result may be deemed to have voting and dispositive power over the securities held directly by the DAFNA Funds. The address of the selling stockholders is c/o DAFNA Capital Management LLC, 10990 Wilshire Blvd., Suite 1400, Los Angeles, CA 90024.
- (12) Consists of 148,260 shares of common stock and warrants to purchase up to an aggregate of 44,478 shares of common stock held directly by Sphera Biotech Master Fund, L.P. Doron Breen directly or indirectly controls Sphera Biotech Master Fund, L.P. and as a result may be deemed to have voting and dispositive power over the securities held directly by Sphera Biotech Master Fund, L.P. The address of the selling stockholder is c/o Sphera Global Healthcare Management, 21 Ha'arbaa Street, Tel Aviv, Israel.
- (13) Consists of 98,840 shares of common stock and warrants to purchase up to an aggregate of 29,652 shares of common stock held directly by CVI Investments, Inc. ("CVI"). Heights Capital Management, Inc., the authorized agent of CVI, has discretionary authority to vote and dispose of the shares held directly by CVI and may be deemed to be the beneficial owner of these shares. Martin Kobinger, in his capacity as Investment Manager of Heights Capital Management, Inc., may also be deemed to have investment discretion and voting power over the shares held by CVI. Mr. Kobinger disclaims any such beneficial ownership of the shares. CVI is affiliated with one or more FINRA members, none of whom are currently expected to participate in any sale pursuant to this prospectus contained in the related registration statement on Form S-1. The address of the selling stockholder is c/o Heights Capital Management, Suite 3250, San Francisco, CA 94111.
- (14) Consists of (i) 28,660 shares of common stock and warrants to purchase up to an aggregate of 8,598 shares of common stock held directly by Monashee Solitario Fund LP ("Solitario"), (ii) 21,750 shares of common stock and warrants to purchase up to an aggregate of 6,525 shares of common stock held directly by Monashee Pure Alpha SPV I LP ("Pure Alpha") and (iii) 48,430 shares of common stock and warrants to purchase up to an aggregate of 14,529 shares of common stock held directly by BEMAP Master Fund LTD ("BEMAP" and together with Solitario and Pure Alpha, the "Monashee Funds"). Jeff Muller, CCO of Monashee Investment Management LLC, directly or indirectly controls the Monashee Funds and as a result may be deemed to have voting and dispositive power over the securities held directly by the Monashee Funds. The address of the selling stockholders is c/o Monashee Investment Management LLC, 75 Park Plaza, 2nd Floor, Boston, MA 02116.
- (15) Consists of 49,410 shares of common stock and warrants to purchase up to an aggregate of 14,823 shares of common stock held directly by Driehaus Life Sciences Master Fund, L.P. Michael Caldwell directly or indirectly controls Driehaus Life Sciences Master Fund, L.P. and as a result may be deemed to have voting and dispositive power over the securities held directly by Driehaus Life Sciences Master Fund, L.P. The address of the selling stockholder is Driehaus Life Sciences Master Fund, L.P., 25 E. Erie, Chicago, IL 60611.

PLAN OF DISTRIBUTION

We are registering the shares of common stock issued to the selling stockholders and issuable upon exercise of the warrants and prefunded warrants issued to the selling stockholders to permit the resale of these shares of common stock by the holders of the shares of common stock, warrants and prefunded warrants from time to time after the date of this prospectus. We will not receive any of the proceeds from the sale by the selling stockholders of the shares of common stock. We will bear all fees and expenses incident to our obligation to register the shares of common stock.

The selling stockholders may sell all or a portion of the shares of common stock beneficially owned by them and offered hereby from time to time directly or through one or more underwriters, broker-dealers or agents. If the shares of common stock are sold through underwriters or broker-dealers, the selling stockholders will be responsible for underwriting discounts or commissions or agent's commissions. The shares of common stock may be sold on any national securities exchange or quotation service on which the securities may be listed or quoted at the time of sale, in the over-the-counter market or in transactions otherwise than on these exchanges or systems or in the over-the-counter market and in one or more transactions at fixed prices, at prevailing market prices at the time of the sale, at varying prices determined at the time of sale, or at negotiated prices. These sales may be effected in transactions, which may involve crosses or block transactions. The selling stockholders may use any one or more of the following methods when selling shares:

- ordinary brokerage transactions and transactions in which the broker-dealer solicits purchasers;
- block trades in which the broker-dealer will attempt to sell the shares as agent but may position and resell a portion of the block as principal to facilitate the transaction;
- purchases by a broker-dealer as principal and resale by the broker-dealer for its account;
- an exchange distribution in accordance with the rules of the applicable exchange;
- privately negotiated transactions;
- settlement of short sales entered into after the effective date of the registration statement of which this prospectus is a part;
- broker-dealers may agree with the selling stockholders to sell a specified number of such shares at a stipulated price per share;
- through the writing or settlement of options or other hedging transactions, whether such options are listed on an options exchange or otherwise;
- a combination of any such methods of sale; and
- any other method permitted pursuant to applicable law.

The selling stockholders also may resell all or a portion of the shares in open market transactions in reliance upon Rule 144 under the Securities Act, as permitted by that rule, or Section 4(a)(1) under the Securities Act, if available, rather than under this prospectus, provided that they meet the criteria and conform to the requirements of those provisions.

Broker-dealers engaged by the selling stockholders may arrange for other broker-dealers to participate in sales. If the selling stockholders effect such transactions by selling shares of common stock to or through underwriters, broker-dealers or agents, such underwriters, broker-dealers or agents may receive commissions in the form of discounts, concessions or commissions from the selling stockholders or commissions from purchasers of the shares of common stock for whom they may act as agent or to whom they may sell as principal. Such commissions will be in amounts to be negotiated, but, except as set forth in a supplement to this Prospectus, in the case of an agency transaction will not be in excess of a customary brokerage commission in compliance with FINRA Rule 2440; and in the case of a principal transaction a markup or markdown in compliance with FINRA IM-2440.

In connection with sales of the shares of common stock or otherwise, the selling stockholders may enter into hedging transactions with broker-dealers or other financial institutions, which may in turn engage in short sales of the shares of common stock in the course of hedging in positions they assume. The selling stockholders may also sell shares of common stock short and if such short sale shall take place after the date that this Registration Statement is declared effective by the Commission, the selling stockholders may deliver shares of common stock covered by this prospectus to close out short positions and to return borrowed shares in connection with such short sales. The selling stockholders may also loan or pledge shares of common stock to broker-dealers that in turn may sell such shares, to the extent permitted by applicable law. The selling stockholders may also enter into option or other transactions with broker-dealers or other financial institutions or the creation of one or more derivative securities which require the delivery to such broker-dealer or other financial institution of shares offered by this prospectus, which shares such broker-dealer or other financial institution may resell pursuant to this prospectus (as supplemented or amended to reflect such transaction). Notwithstanding the foregoing, the selling stockholders have been advised that they may not use shares registered on this registration statement to cover short sales of our common stock made prior to the date the registration statement, of which this prospectus forms a part, has been declared effective by the SEC.

The selling stockholders may, from time to time, pledge or grant a security interest in some or all of the warrants, prefunded warrants or shares of common stock owned by them and, if they default in the performance of their secured obligations, the pledgees or secured parties may offer and sell the shares of common stock from time to time pursuant to this prospectus or any amendment to this prospectus under Rule 424(b)(3) or other applicable provision of the Securities Act, amending, if necessary, the list of selling stockholders to include the pledgee, transferee or other successors in interest as selling stockholders under this prospectus. The selling stockholders also may transfer and donate the shares of common stock in other circumstances in which case the transferees, donees, pledgees or other successors in interest will be the selling beneficial owners for purposes of this prospectus.

The selling stockholders and any broker-dealer or agents participating in the distribution of the shares of common stock may be deemed to be "underwriters" within the meaning of Section 2(a)(11) of the Securities Act in connection with such sales. In such event, any commissions paid, or any discounts or concessions allowed to, any such broker-dealer or agent and any profit on the resale of the shares purchased by them may be deemed to be underwriting commissions or discounts under the Securities Act. Selling Stockholders who are "underwriters" within the meaning of Section 2(a)(11) of the Securities Act will be subject to the applicable prospectus delivery requirements of the Securities Act including Rule 172 thereunder and may be subject to certain statutory liabilities of, including but not limited to, Sections 11, 12 and 17 of the Securities Act and Rule 10b-5 under the Exchange Act.

Each selling stockholder has informed the Company that it is not a registered broker-dealer and does not have any written or oral agreement or understanding, directly or indirectly, with any person to

distribute the common stock. Upon the Company being notified in writing by a selling stockholder that any material arrangement has been entered into with a broker-dealer for the sale of common stock through a block trade, special offering, exchange distribution or secondary distribution or a purchase by a broker or dealer, a supplement to this prospectus will be filed, if required, pursuant to Rule 424(b) under the Securities Act, disclosing (i) the name of each such selling stockholder and of the participating broker-dealer(s), (ii) the number of shares involved, (iii) the price at which such the shares of common stock were sold, (iv) the commissions paid or discounts or concessions allowed to such broker-dealer(s), where applicable, (v) that such broker-dealer(s) did not conduct any investigation to verify the information set out or incorporated by reference in this prospectus, and (vi) other facts material to the transaction. In no event shall any broker-dealer receive fees, commissions and markups, which, in the aggregate, would exceed eight percent (8.0%).

Under the securities laws of some states, the shares of common stock may be sold in such states only through registered or licensed brokers or dealers. In addition, in some states the shares of common stock may not be sold unless such shares have been registered or qualified for sale in such state or an exemption from registration or qualification is available and is complied with.

There can be no assurance that any selling stockholder will sell any or all of the shares of common stock registered pursuant to the registration statement, of which this prospectus forms a part.

Each selling stockholder and any other person participating in such distribution will be subject to applicable provisions of the Exchange Act and the rules and regulations thereunder, including, without limitation, to the extent applicable, Regulation M of the Exchange Act, which may limit the timing of purchases and sales of any of the shares of common stock by the selling stockholder and any other participating person. To the extent applicable, Regulation M may also restrict the ability of any person engaged in the distribution of the shares of common stock to engage in market-making activities with respect to the shares of common stock. All of the foregoing may affect the marketability of the shares of common stock and the ability of any person or entity to engage in market-making activities with respect to the shares of common stock.

We will pay all expenses of the registration of the shares of common stock pursuant to the registration rights agreement, including, without limitation, Securities and Exchange Commission filing fees and expenses of compliance with state securities or "blue sky" laws; *provided, however*, that each selling stockholder will pay all underwriting discounts and selling commissions, if any and any related legal expenses incurred by it. We will indemnify the selling stockholders against certain liabilities, including some liabilities under the Securities Act, in accordance with the registration rights agreement, or the selling stockholders will be entitled to contribution. We may be indemnified by the selling stockholders against civil liabilities, including liabilities under the Securities Act, that may arise from any written information furnished to us by the selling stockholders specifically for use in this prospectus, in accordance with the related registration rights agreements, or we may be entitled to contribution.

LEGAL MATTERS

Certain legal matters relating to the issuance of the securities offered by this prospectus will be passed upon for us by Wilson Sonsini Goodrich & Rosati, Professional Corporation, Seattle, Washington.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on [Form 10-K](#) for the year ended December 31, 2020, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

This prospectus does not include all of the information contained in the registration statement. You should refer to the registration statement and its exhibits for additional information. Whenever we make reference in this prospectus to any of our contracts, agreements or other documents, the references are not necessarily complete and you should refer to the exhibits filed as part of the registration statement for copies of the actual contract, agreement or other document.

We file annual, quarterly and other reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at <http://www.sec.gov>. Our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q and Current Reports on Form 8-K, including any amendments to those reports, and other information that we file with or furnish to the SEC pursuant to Section 13(a) or 15(d) of the Exchange Act, can also be accessed free of charge from our website at <http://www.alpineimmunesciences.com>. These filings will be available as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. Information contained on our website is not part of this prospectus.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

We have elected to incorporate the following documents into this prospectus, together with all exhibits filed therewith or incorporated therein by reference, to the extent not otherwise amended or superseded by the contents of this prospectus:

- our Annual Report on [Form 10-K](#) for the year ended December 31, 2020, as filed with the SEC on March 18, 2021;
- our Quarterly Report on [Form 10-Q](#) for the three months ended March 31, 2021, as filed with the SEC on May 13, 2021; and
- the description of our common stock contained in our Registration Statement on [Form 8-A](#), as filed with the SEC on June 16, 2015 (File No. 001-37449), including any amendment or report filed for the purpose of updating such description.

In addition, we incorporate by reference in this prospectus any future filings we make with the SEC under Sections 13(a), 13(c), 14, or 15(d) of the Exchange Act (excluding any information furnished and not filed with the SEC) after the date on which the registration statement that includes this prospectus was initially filed with the SEC (including all such documents we may file with the SEC after the date of the initial registration statement and until all offerings under this prospectus are terminated).

Any statement contained in a document incorporated by reference herein shall be deemed to be modified or superseded for all purposes to the extent that a statement contained in this prospectus or in any other subsequently filed document which is also incorporated or deemed to be incorporated by reference, modifies or supersedes such statement. Any statement so modified or superseded shall not be deemed, except as so modified or superseded, to constitute a part of this prospectus.

We will provide to each person, including any beneficial owner, to whom this prospectus is delivered, upon written or oral request, at no cost to the requester, a copy of any and all of the information that is incorporated by reference in this prospectus.

Requests for such documents should be directed to:

Alpine Immune Sciences, Inc.
Attn: Investor Relations
188 East Blaine Street, Suite 200
Seattle, Washington 98102
(206) 788-4545

The SEC maintains a website that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC at <http://www.sec.gov>. You may also access the documents incorporated by reference in this prospectus through our website at www.alpineimmunesciences.com. Except for the specific incorporated documents listed above, no information available on or through our website shall be deemed to be incorporated in this prospectus or the registration statement of which it forms a part. Information contained on our website is not part of this prospectus.



7,709,416 Shares of Common Stock

PROSPECTUS

May 18, 2021