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

FORM S-3
REGISTRATION STATEMENT
Under
The Securities Act of 1933

DENALI THERAPEUTICS INC.
(Exact name of Registrant as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

46-3872213
(I.R.S. Employer
Identification No.)

**161 Oyster Point Blvd.
South San Francisco, CA, 94080
(650) 866-8548**

(Address, including zip code, and telephone number, including area code, of Registrant's principal executive offices)

**Ryan J. Watts, Ph.D.
President and Chief Executive Officer
Denali Therapeutics Inc.
161 Oyster Point Blvd.
South San Francisco, California 94080
(650) 866-8548**

(Name, address, including zip code, and telephone number, including area code, of agent for service)

**Copies to:
Tony Jeffries
Jennifer Knapp
Wilson Sonsini Goodrich & Rosati, P.C.
650 Page Mill Road
Palo Alto, California 94304
(650) 493-9300**

**APPROXIMATE DATE OF COMMENCEMENT OF PROPOSED SALE TO THE PUBLIC:
From time to time after the effective date of this Registration Statement.**

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box.

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering.

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective on filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box.

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer

Accelerated filer

Non-accelerated filer

Smaller reporting company

Emerging growth company

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 7(a)(2)(B) of the Securities Act.

CALCULATION OF REGISTRATION FEE

| Title of each class of securities to be registered | Amount to be registered/proposed maximum offering price per unit/proposed maximum aggregate offering price (1)(2) | Amount of registration fee (3) |
|--|---|--------------------------------|
| Common Stock, \$0.01 par value | | |
| Preferred Stock, \$0.01 par value | | |
| Debt Securities | | |
| Warrants | | |
| Purchase Contracts | | |
| Units | | |
| Total | | |

(1) Omitted pursuant to Form S-3 General Instruction II.E.

(2) An unspecified number of securities or aggregate principal amount, as applicable, is being registered as may from time to time be offered at unspecified prices.

(3) In accordance with Rules 456(b) and 457(r) under the Securities Act of 1933, as amended, the registrant is deferring payment of the registration fee.

DENALI THERAPEUTICS INC.



**Common Stock
Preferred Stock
Debt Securities
Warrants
Purchase Contracts
Units**

We may offer and sell the securities identified above from time to time in one or more offerings. This prospectus provides you with a general description of the securities.

Each time we offer and sell securities, we will provide a supplement to this prospectus that contains specific information about the offering and the amounts, prices and terms of the securities. The supplement may also add, update or change information contained in this prospectus with respect to that offering. You should carefully read this prospectus and the applicable prospectus supplement, together with any documents we incorporated by reference, before you invest in any of our securities.

We may offer and sell the securities described in this prospectus and any prospectus supplement to or through one or more underwriters, dealers and agents, or directly to purchasers, or through a combination of these methods. If any underwriters, dealers or agents are involved in the sale of any of the securities, their names and any applicable purchase price, fee, commission or discount arrangement between or among them will be set forth, or will be calculable from the information set forth, in the applicable prospectus supplement. See the sections of this prospectus entitled "About this Prospectus" and "Plan of Distribution" for more information. No securities may be sold without delivery of this prospectus and the applicable prospectus supplement describing the method and terms of the offering of such securities.

INVESTING IN OUR SECURITIES INVOLVES RISKS. SEE "RISK FACTORS" BEGINNING ON PAGE 3 OF THIS PROSPECTUS AND IN ANY SIMILAR SECTION CONTAINED IN OR INCORPORATED BY REFERENCE HEREIN OR IN THE APPLICABLE PROSPECTUS SUPPLEMENT CONCERNING FACTORS YOU SHOULD CONSIDER BEFORE INVESTING IN OUR SECURITIES.

Our common stock is listed on The Nasdaq Global Select Market ("Nasdaq") under the symbol "DNLI." On March 11, 2019, the last reported sale price of our common stock on NASDAQ was \$21.81 per share.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

The date of this prospectus is March 12, 2019.

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ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the U.S. Securities and Exchange Commission (the "SEC") as a "well-known seasoned issuer" as defined in Rule 405 under the Securities Act of 1933, as amended, using a "shelf" registration process. By using a shelf registration statement, we may sell securities from time to time and in one or more offerings as described in this prospectus. Each time that we offer and sell securities, we will provide a prospectus supplement to this prospectus that contains specific information about the securities being offered and sold and the specific terms of that offering and, to the extent appropriate, any updates to the information about us contained in this prospectus. We may also authorize one or more free writing prospectuses to be provided to you that may contain material information relating to these offerings. The prospectus supplement may also add, update or change information contained in this prospectus with respect to that offering. If there is any inconsistency between the information in this prospectus and the applicable prospectus supplement, you should rely on the prospectus supplement. Before purchasing any securities, you should carefully read both this prospectus and the applicable prospectus supplement, together with the additional information described under the heading "Where You Can Find More Information" and "Incorporation by Reference."

We have not authorized anyone to provide you with any information or to make any representations other than those contained in this prospectus, any applicable prospectus supplement or 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. We will not make an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus and the applicable prospectus supplement to this prospectus is accurate as of the date on its respective cover or as otherwise specified therein and that any information incorporated by reference is accurate only as of the date of the document incorporated by reference, unless we indicate otherwise. Our business, financial condition, results of operations and prospects may have changed since those dates. This prospectus incorporates by reference, and any prospectus supplement or free writing prospectus may contain and incorporate by reference, market data and industry statistics and forecasts that are based on independent industry publications and other publicly available information. Although we believe these sources are reliable, we do not guarantee the accuracy or completeness of this information and we have not independently verified this information. Although we are not aware of any misstatements regarding the market and industry data presented in this prospectus and the documents incorporated herein by reference, these estimates involve risks and uncertainties and are subject to change based on various factors, including those discussed under the heading "Risk Factors" contained or incorporated by reference in this prospectus, the applicable prospectus supplement and any related free writing prospectus and under similar headings in other documents that are incorporated by reference into this prospectus. Accordingly, investors should not place undue reliance on this information.

When we refer to "Denali," "we," "our," "us" and the "Company" in this prospectus, we mean Denali Therapeutics Inc., unless the context indicates otherwise or unless otherwise specified. When we refer to "you," we mean the holders of the applicable series of securities.

THE COMPANY

Denali is a biopharmaceutical company developing a broad portfolio of therapeutic candidates for neurodegenerative diseases. Denali pursues new treatments by rigorously assessing genetically validated targets, engineering delivery across the blood-brain barrier and guiding development with biomarker monitoring to demonstrate target engagement and select patients.

We were incorporated in the State of Delaware in 2013. Our principal executive offices are located at 161 Oyster Point Blvd., South San Francisco, California 94080. Our telephone number is (650) 866-8548. Our website address is www.denalitherapeutics.com. We also use our website as a means of disclosing material non-public information and for complying with our disclosure obligations under Regulation FD.

RISK FACTORS

Investing in our securities involves a high degree of risk. Before making a decision to invest in our securities, in addition to carefully considering the other information contained in this prospectus, in any accompanying prospectus supplement and incorporated by reference herein or therein, you should carefully consider the risks described under the caption "Risk Factors" contained in the applicable prospectus supplement, and any related free writing prospectus, and the risks discussed under the caption "Risk Factors" contained in our most recent annual report on Form 10-K and in our most recent quarterly report on Form 10-Q, as well as any amendments thereto, which are incorporated by reference into this prospectus in their entirety, together with other information in this prospectus, the documents incorporated by reference, and any free writing prospectus that we may authorize for use in connection with a specific offering. See "Where You Can Find More Information; Incorporation by Reference."

USE OF PROCEEDS

We intend to use the net proceeds from the sale of the securities as set forth in the applicable prospectus supplement.

DESCRIPTION OF SECURITIES

We may issue from time to time, in one or more offerings, the following securities:

- shares of common stock, par value \$0.01 per share, of the Company;
- shares of preferred stock, par value \$0.01 per share, of the Company;
- debt securities, which may be senior or subordinated, and which may be convertible into our common stock or be non-convertible;
- warrants to purchase from us shares of our common stock or preferred stock or other securities;
- purchase contracts; and
- units representing two or more of the foregoing securities.

We will set forth in the applicable prospectus supplement and/or free writing prospectus a description of any common stock, debt securities, warrants, purchase contracts or units issued by us that may be offered or sold pursuant to this prospectus. The terms of the offering of securities, the initial offering price and the net proceeds to us will be contained in the prospectus supplement, and other offering material, relating to such offer.

PLAN OF DISTRIBUTION

We may sell the offered securities from time to time:

- through underwriters or dealers;
- through agents;
- directly to one or more purchasers; or
- through a combination of any of these methods of sale.

We will identify the specific plan of distribution, including any underwriters, dealers, agents or direct purchasers and their compensation in the applicable prospectus supplement.

LEGAL MATTERS

Wilson Sonsini Goodrich & Rosati, Professional Corporation, Palo Alto, California, will pass upon certain legal matters relating to the issuance and sale of the securities offered hereby on behalf of Denali Therapeutics Inc. Additional legal matters may be passed upon for us or any underwriters, dealers or agents, by counsel that we will name in the applicable prospectus supplement.

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, 2018, 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

We file periodic and current reports, proxy statements and other information with the SEC. Information filed with the SEC by us can be inspected and copied at the Public Reference Room maintained by the SEC at 100 F Street, N.E., Washington, D.C. 20549. You may also obtain copies of this information by mail from the Public Reference Room of the SEC at prescribed rates. Further information on the operation of the SEC's Public Reference Room in Washington, D.C. can be obtained by calling the SEC at 1-800-SEC-0330. The SEC also maintains a web site that contains reports, proxy and information statements and other information about issuers, such as us, who file electronically with the SEC. The address of that website is <http://www.sec.gov>.

Our web site address is www.denalitherapeutics.com. The information on our web site, or that can be accessed through our web site, however, is not, and should not be deemed to be, a part of this prospectus.

This prospectus and any prospectus supplement are part of a registration statement that we filed with the SEC and do not contain all of the information in the registration statement. The full registration statement may be obtained from the SEC or us, as provided below. Forms of the indenture and other documents establishing the terms of the offered securities are or may be filed as exhibits to the registration statement. Statements in this prospectus or any prospectus supplement about these documents are summaries and each statement is qualified in all respects by reference to the document to which it refers. You should refer to the actual documents for a more complete description of the relevant matters. You may inspect a copy of the registration statement at the SEC's Public Reference Room in Washington, D.C. or through the SEC's website, as provided above.

INCORPORATION BY REFERENCE

The SEC's rules allow us to "incorporate by reference" information into this prospectus, which means that we can disclose important information to you by referring you to another document filed separately with the SEC. The information incorporated by reference is deemed to be part of this prospectus, and subsequent information that we file with the SEC will automatically update and supersede that information. Any statement contained in a previously filed document incorporated by reference will be deemed to be modified or superseded for purposes of this prospectus to the extent that a statement contained in this prospectus modifies or replaces that statement.

We incorporate by reference our documents listed below and any future filings made by us with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, which we refer to as the "Exchange Act" in this prospectus, between the date of this prospectus and the termination of the offering of the securities described in this prospectus. We are not, however, incorporating by reference any documents or portions thereof, whether specifically listed below or filed in the future, that are not deemed "filed" with the SEC, including any information furnished pursuant to Items 2.02 or 7.01 of Form 8-K or related exhibits furnished pursuant to Item 9.01 of Form 8-K.

This prospectus and any accompanying prospectus supplement incorporate by reference the documents set forth below that have previously been filed with the SEC:

- Our Annual Report on Form 10-K for the fiscal year ended December 31, 2018 filed on March 12, 2019.
- Our Current Report on Form 8-K filed on January 4, 2019, and our Current Report on Form 8-K filed on March 12, 2019.
- The description of our common stock, par value \$0.01 per share, contained in our registration statement on Form 8-A, filed with the SEC on November 30, 2017, including any subsequent filed amendments and reports updating such description.

All reports and other documents we subsequently file pursuant to Section 13(a), 13(c), 14 or 15(d) of the Exchange Act prior to the termination of this offering but excluding any information furnished to, rather than filed with, the SEC, will also be incorporated by reference into this prospectus and deemed to be part of this prospectus from the date of the filing of such reports and documents.

You may request a free copy of any of the documents incorporated by reference in this prospectus (other than exhibits, unless they are specifically incorporated by reference in the documents) by writing or telephoning us at the following address:

Denali Therapeutics Inc.
161 Oyster Point Blvd.
South San Francisco, California 94080
(650) 866-8548

Exhibits to the filings will not be sent, however, unless those exhibits have specifically been incorporated by reference in this prospectus and any accompanying prospectus supplement.

The information accessible through any website referred to in this prospectus or any document incorporated herein is not, and should not be deemed to be, a part of this prospectus.

PART II
INFORMATION NOT REQUIRED IN PROSPECTUS

Item 14. Other Expenses of Issuance and Distribution

The following is an estimate of the expenses (all of which are to be paid by the registrant) that we may incur in connection with the securities being registered hereby.

| | |
|---|---------------|
| SEC registration fee | \$ (1)(2) |
| Printing expenses | (2) |
| Legal fees and expenses (including Blue Sky fees) | (2) |
| Accounting fees and expenses | (2) |
| Transfer agent, trustee and warrant agent fees and expenses | (2) |
| Miscellaneous | (2) |
| Total | \$ (2) |

- (1) Pursuant to Rules 456(b) and 457(r) under the Securities Act of 1933, as amended, the SEC registration fee will be paid at the time of any particular offering of securities under the registration statement, and is therefore not currently determinable.
- (2) These fees and expenses are calculated based on the securities offered and the number of issuances and accordingly cannot be estimated at this time.

Item 15. Indemnification of Directors and Officers

The registrant is a Delaware corporation. Section 145(a) of the Delaware General Corporation Law, or the DGCL, provides that a Delaware corporation may indemnify any person who was or is a party or is threatened to be made a party to any threatened, pending or completed action, suit or proceeding, whether civil, criminal, administrative or investigative, other than an action by or in the right of the corporation, by reason of the fact that such person is or was a director, officer, employee or agent of the corporation, or is or was serving at the request of the corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise, against expenses (including attorney fees), judgments, fines and amounts paid in settlement actually and reasonably incurred by the person in connection with such action, suit or proceeding if the person acted in good faith and in a manner the person reasonably believed to be in or not opposed to the best interests of the corporation, and, with respect to any criminal action or proceeding, had no reasonable cause to believe his or her conduct was unlawful.

Section 145(b) of the DGCL provides that a Delaware corporation may indemnify any person who was or is a party or is threatened to be made a party to any threatened, pending or completed action or suit by or in the right of the corporation to procure a judgment in its favor by reason of the fact that such person acted in any of the capacities set forth above, against expenses (including attorney fees) actually and reasonably incurred by such person in connection with the defense or settlement of such action or suit if the person acted in good faith and in a manner the person reasonably believed to be in or not opposed to the best interests of the corporation, except that no indemnification shall be made in respect of any claim, issue or matter as to which such person shall have been adjudged to be liable to the corporation, unless and only to the extent that the Court of Chancery or the court in which such action or suit was brought shall determine that, despite the adjudication of liability but in view of all the circumstances of the case, such person is fairly and reasonably entitled to indemnification for such expenses which the court shall deem proper.

Further subsections of DGCL Section 145 provide that:

- (1) to the extent a present or former director or officer of a corporation has been successful on the merits or otherwise in the defense of any action, suit or proceeding referred to in subsections (a) and (b) of Section 145 or in the defense of any claim, issue or matter therein, such person shall be indemnified against expenses, including attorneys' fees, actually and reasonably incurred by such person in connection therewith;
- (2) the indemnification and advancement of expenses provided for pursuant to Section 145 shall not be deemed exclusive of any other rights to which those seeking indemnification or advancement of expenses may be entitled under any bylaw, agreement, vote of stockholders or disinterested directors or otherwise; and
- (3) the corporation shall have the power to purchase and maintain insurance on behalf of any person who is or was a director, officer, employee or agent of the corporation, or is or was serving at the request of the corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise, against any liability asserted against such person and incurred by such person in any such capacity, or arising out of such person's status as such, whether or not the corporation would have the power to indemnify such person against such liability under Section 145.

As used in this Item 15, the term "proceeding" means any threatened, pending, or completed action, suit, or proceeding, whether or not by or in the right of the registrant, and whether civil, criminal, administrative, investigative or otherwise.

Section 145 of the DGCL makes provision for the indemnification of officers and directors in terms sufficiently broad to indemnify officers and directors of the registrant under certain circumstances from liabilities (including reimbursement for expenses incurred) arising under the Securities Act of 1933, as amended, or the Securities Act. The registrant's amended and restated certificate of incorporation provides, in effect, that, to the fullest extent and under the circumstances permitted by Section 145 of the DGCL, the registrant will indemnify any and all of its executive officers and directors. The registrant may, in its discretion, similarly indemnify its employees and agents. The registrant's amended and restated certificate of incorporation also relieves its directors from monetary damages to registrant or its stockholders for breach of such director's fiduciary duty as a director to the fullest extent permitted by the DGCL. Under Section 102(b)(7) of the DGCL, a corporation may relieve its directors from personal liability to such corporation or its stockholders for monetary damages for any breach of their fiduciary duty as directors except (1) for a breach of the duty of loyalty, (2) for failure to act in good faith, (3) for intentional misconduct or knowing violation of law, (4) for willful or negligent violations of certain provisions in the DGCL imposing certain requirements with respect to stock repurchases, redemptions and dividends, or (5) for any transactions from which the director derived an improper personal benefit.

The registrant has entered into indemnification agreements with its directors and executive officers that provide, in general, that the registrant will indemnify them to the fullest extent permitted by law in connection with their service to the registrant or on the registrant's behalf. The registrant intends to enter into indemnification agreements with any new directors and executive officers in the future.

The registrant has purchased and intends to maintain insurance on behalf of each and any person who is or was a director or officer of the Company against any loss arising from any claim asserted against him or her and incurred by him or her in any such capacity, subject to certain exclusions.

See also the undertakings set out in response to Item 17 herein.

Item 16. Exhibits

(a) Exhibits

A list of exhibits filed with this registration statement on Form S-3 is set forth on the Exhibit Index and is incorporated herein by reference.

Item 17. Undertakings

(a) The undersigned registrant hereby undertakes:

(1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement:

(i) To include any prospectus required by Section 10(a)(3) of the Securities Act of 1933;

(ii) To reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement; and

(iii) To include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement;

provided, however, that paragraphs (a)(1)(i), (a)(1)(ii), and (a)(1)(iii) above do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or furnished to the Commission by the registrant pursuant to section 13 or section 15(d) of the Securities Exchange Act of 1934 that are incorporated by reference in the registration statement, or is contained in a form of prospectus filed pursuant to Rule 424(b) that is a part of the registration statement.

(2) That, for the purpose of determining any liability under the Securities Act of 1933, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

(3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

(4) That, for the purpose of determining liability under the Securities Act of 1933 to any purchaser:

(A) Each prospectus filed by the registrant pursuant to Rule 424(b)(3) shall be deemed to be part of the registration statement as of the date the filed prospectus was deemed part of and included in the registration statement; and

(B) Each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5), or (b)(7) as part of a registration statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vi), or (x) for the purpose of providing the information required by section 10(a) of the Securities Act of 1933 shall be deemed to be part of and included in the registration statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in the prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a new effective date of the registration statement relating to the securities in the registration statement to which that prospectus relates, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof. Provided, however, that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such effective date.

(C) Each prospectus filed pursuant to Rule 424(b) as part of a registration statement relating to an offering, other than registration statements relying on Rule 430B or other than prospectuses filed in reliance on Rule 430A, shall be deemed to be part of and included in the registration statement as of the date it is first used after effectiveness. Provided, however, that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such first use, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such date of first use.

(5) That, for the purpose of determining liability of the registrant under the Securities Act of 1933 to any purchaser in the initial distribution of securities:

The undersigned registrant undertakes that in a primary offering of securities of the undersigned registrant pursuant to this registration statement, regardless of the underwriting method used to sell the securities to the purchaser, if the securities are offered or sold to such purchaser by means of any of the following communications, the undersigned registrant will be a seller to the purchaser and will be considered to offer or sell such securities to such purchaser:

(i) Any preliminary prospectus or prospectus of the undersigned registrant relating to the offering required to be filed pursuant to Rule 424;

(ii) Any free writing prospectus relating to the offering prepared by or on behalf of the undersigned registrant or used or referred to by the undersigned registrant;

(iii) The portion of any other free writing prospectus relating to the offering prepared by or on behalf of the undersigned registrant or its securities provided by or on behalf of the undersigned registrant; and

(iv) Any other communications that is an offer in the offering made by the undersigned registrant to the purchaser.

(6) To file an application for the purpose of determining the eligibility of the trustee to act under subsection (a) of Section 310 of the Trust Indenture Act in accordance with the rules and regulations prescribed by the Commission under Section 305(b)(2) of the Trust Indenture Act.

(b) The undersigned registrant hereby undertakes that, for purposes of determining any liability under the Securities Act of 1933, each filing of the registrant's annual report pursuant to Section 13(a) or Section 15(d) of the Securities Exchange Act of 1934 (and, where applicable, each filing of an employee benefit plan's annual report pursuant to section 15(d) of the Securities Exchange Act of 1934) that is incorporated by reference in the registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

(c) Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

The undersigned registrant hereby undertakes that:

- (1) For purposes of determining any liability under the Securities Act of 1933, the information omitted from the form of prospectus filed as part of this registration statement in reliance upon Rule 430A and contained in a form of prospectus filed by the registrant pursuant to Rule 424(b) (1) or (4) or 497(h) under the Securities Act shall be deemed to be part of this registration statement as of the time it was declared effective.
- (2) For the purpose of determining any liability under the Securities Act of 1933, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

EXHIBIT INDEX

| Exhibit Number | Description | Incorporated by Reference | | | |
|----------------|---|---------------------------|------------|---------|-------------|
| | | Form | File No. | Exhibit | Filing Date |
| 1.1* | Form of Underwriting Agreement. | | | | |
| 3.1 | Amended and Restated Certificate of Incorporation of the Registrant. | 8-K | 001-38311 | 3.1 | 12/12/2017 |
| 3.2 | Amended and Restated Bylaws of the Registrant. | 8-K | 001-38311 | 3.2 | 12/12/2017 |
| 4.1 | Investors' Rights Agreement among the Registrant and certain of its stockholders, dated May 8, 2015, as amended on June 4, 2015, July 22, 2015 and June 22, 2016. | S-1 | 333-221522 | 4.1 | 11/13/2017 |
| 4.2 | Specimen common stock certificate of the Registrant. | S-1/A | 333-221522 | 4.2 | 11/27/2017 |
| 4.3* | Form of Indenture. | | | | |
| 4.4* | Form of Note. | | | | |
| 4.5* | Form of Warrant. | | | | |
| 4.6* | Form of Warrant Agreement. | | | | |
| 4.7* | Form of Purchase Contract Agreement. | | | | |
| 4.8* | Form of Unit Agreement. | | | | |
| 5.1 | Opinion of Wilson Sonsini Goodrich & Rosati, Professional Corporation. | | | | |
| 23.1 | Consent of Wilson Sonsini Goodrich & Rosati, Professional Corporation (included in Exhibit 5.1). | | | | |
| 23.2 | Consent of Independent Registered Public Accounting Firm. | | | | |
| 24.1 | Powers of Attorney (incorporated by reference to the signature page hereto). | | | | |
| 25.1** | Statement of Eligibility on Form T-1 under the Trust Indenture Act of 1939, as amended, of the trustee under the indenture filed as Exhibit 4.1 above. | | | | |
| | • To be filed by amendment or incorporated by reference in connection with the offering of the securities. | | | | |
| | ** To be filed pursuant to Section 305(b)(2) of the Trust Indenture Act of 1939. | | | | |

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, as amended, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this registration statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of South San Francisco, State of California, on the 12th day of March, 2019.

DENALI THERAPEUTICS INC.

By: /s/ Ryan J. Watts

Ryan J. Watts, Ph.D.

President and Chief Executive Officer

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below constitutes and appoints Ryan J. Watts, Ph.D. and Steve E. Krognos or either of them, as his or her true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution, for him or her and in his or her name, place and stead, in any and all capacities, to file and sign any and all amendments, including post-effective amendments and any registration statement for the same offering that is to be effective under Rule 462(b) of the Securities Act, as amended, to this registration statement, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or their substitute or substitutes may lawfully do or cause to be done by virtue hereof. This power of attorney shall be governed by and construed with the laws of the State of Delaware and applicable federal securities laws.

Pursuant to the requirements of the Securities Act of 1933, as amended, this registration statement has been signed below by the following persons on behalf of the registrant in the capacities and on the dates indicated.

| Signature | Title | Date |
|--|---|----------------|
| <u>/s/ Ryan J. Watts</u> Ryan J. Watts, Ph.D. | President, Chief Executive Officer and Director (Principal Executive Officer) | March 12, 2019 |
| <u>/s/ Steve E. Krognos</u> Steve E. Krognos | Chief Financial Officer and Treasurer (Principal Financial and Accounting Officer) | March 12, 2019 |
| <u>/s/ Vicki Sato</u> Vicki Sato, Ph.D. | Chairperson of our Board of Directors | March 12, 2019 |
| <u>/s/ Marc Tessier-Lavigne</u> Marc Tessier-Lavigne, Ph.D. | Director | March 12, 2019 |
| <u>/s/ Douglas Cole</u> Douglas Cole, M.D. | Director | March 12, 2019 |
| <u>/s/ Jennifer Cook</u> Jennifer Cook | Director | March 12, 2019 |
| <u>/s/ Jay Flatley</u> Jay Flatley | Director | March 12, 2019 |
| <u>/s/ Peter Klein</u> Peter Klein | Director | March 12, 2019 |
| <u>/s/ Robert Nelsen</u> Robert Nelsen | Director | March 12, 2019 |
| <u>/s/ David Schenkein</u> David Schenkein, M.D. | Director | March 12, 2019 |

March 12, 2019

Denali Therapeutics Inc.
161 Oyster Point Blvd.
South San Francisco, California 94080

Ladies and Gentlemen:

Denali Therapeutics Inc., a Delaware corporation (the "**Company**"), is filing with the United States Securities and Exchange Commission a Registration Statement on Form S-3 (the "**Registration Statement**") for the purpose of registering under the Securities Act of 1933, as amended (the "**Securities Act**"), (i) the Company's debt securities (the "**Debt Securities**"), which may be issued pursuant to an indenture, between the Company and a trustee to be named therein (the "**Trustee**") (the "**Indenture**"); (ii) shares of common stock, par value \$0.01 per share (the "**Common Stock**") of the Company; (iii) shares of preferred stock, par value \$0.01 per share (the "**Preferred Stock**") of the Company; (iv) purchase contracts (the "**Purchase Contracts**"), which may be issued under one or more purchase contract agreements (each such Purchase Contract, a "**Purchase Contract Agreement**") to be entered into between the Company and the purchase contract agent to be named therein (the "**Purchase Contract Agent**"); (v) units (the "**Units**") to be issued under one or more unit agreements to be entered into among the Company, a bank or trust company, as unit agent (the "**Unit Agent**"), and the holders from time to time of the Units (each such unit agreement, a "**Unit Agreement**"); and (vi) warrants of the Company (the "**Warrants**"), which may be issued pursuant to a warrant agreement (the "**Warrant Agreement**") between the Company and the warrant agent to be named therein (the "**Warrant Agent**").

We, as your counsel, have examined originals or copies, certified or otherwise identified to our satisfaction, of such documents, corporate records, certificates of public officials and other instruments as we have deemed necessary or advisable for the purpose of rendering this opinion.

Based upon the foregoing, we advise you that, in our opinion:

1. When the specific terms of a particular series of Debt Securities have been duly authorized and established in accordance with the Indenture and such Debt Securities have been duly authorized, executed, authenticated, issued and delivered in accordance with the Indenture and the applicable underwriting or other agreement against payment therefor, such Debt Securities will constitute valid and binding obligations of the Company, enforceable in accordance with their terms, subject to applicable bankruptcy, insolvency and similar laws affecting creditors' rights generally, concepts of reasonableness and equitable principles of general applicability.
2. When the necessary corporate action on the part of the Company has been taken to authorize the issuance and sale of such shares of Common Stock proposed to be sold by the Company, and when such shares of Common Stock are issued and delivered in accordance with the applicable underwriting or other agreement against payment therefor (in excess of par value thereof) or upon conversion or exercise of any security offered under the Registration Statement (the "**Offered Security**"), in accordance with terms of such Offered Security or the instrument governing such Offered Security providing for such conversion or exercise as approved by the Board of Directors of the Company (the "**Board**"), for the consideration approved by the Board (which consideration is not less than the par value of the Common Stock), such shares of Common Stock will be validly issued, fully-paid and non-assessable.
3. Upon designation of the relative rights, preferences and limitations of any series of Preferred Stock by the Board and the proper filing with the Secretary of State of the State of Delaware of a Certificate of Designation relating to such series of Preferred Stock, all necessary corporate action on the part of the Company will have been taken to authorize the issuance and sale of such series of Preferred Stock proposed to be sold by the Company, and when such shares of Preferred Stock are issued and delivered in accordance with the applicable underwriting or other agreement against payment therefor (in excess of par value thereof), such shares of Preferred Stock will be validly issued, fully paid and non-assessable.

4. When the Purchase Contract Agreement to be entered into in connection with the issuance of any Purchase Contracts has been duly authorized, executed and delivered by the Purchase Contract Agent and the Company, the specific terms of the Purchase Contracts have been duly authorized and established in accordance with the Purchase Contract Agreement and such Purchase Contracts have been duly authorized, executed, issued and delivered in accordance with the Purchase Contract Agreement and the applicable underwriting or other agreement against payment therefor, such Purchase Contracts will constitute valid and binding obligations of the Company, enforceable in accordance with their terms, subject to applicable bankruptcy, insolvency and similar laws affecting creditors' rights generally, concepts of reasonableness and equitable principles of general applicability.
5. When the Unit Agreement to be entered into in connection with the issuance of any Units has been duly authorized, executed and delivered by the Unit Agent and the Company, the specific terms of the Units have been duly authorized and established in accordance with the Unit Agreement and such Units have been duly authorized, executed, issued and delivered in accordance with the Unit Agreement and the applicable underwriting or other agreement against payment therefor, such Units will constitute valid and binding obligations of the Company, enforceable in accordance with their terms, subject to applicable bankruptcy, insolvency and similar laws affecting creditors' rights generally, concepts of reasonableness and equitable principles of general applicability.
6. When the Warrant Agreement to be entered into in connection with the issuance of any Warrants has been duly authorized, executed and delivered by the Warrant Agent and the Company, the specific terms of the Warrants have been duly authorized and established in accordance with the Warrant Agreement and such Warrants have been duly authorized, executed, issued and delivered in accordance with the Warrant Agreement and the applicable underwriting or other agreement against payment therefor, such Warrants will constitute valid and binding obligations of the Company, enforceable in accordance with their terms, subject to applicable bankruptcy, insolvency and similar laws affecting creditors' rights generally, concepts of reasonableness and equitable principles of general applicability.

In connection with the opinions expressed above, we have assumed that, at or prior to the time of the delivery of any such security, (i) the Board shall have duly established the terms of such security and duly authorized the issuance and sale of such security and such authorization shall not have been modified or rescinded; (ii) the Company shall remain validly existing as a corporation in good standing under the laws of the State of Delaware; (iii) the Registration Statement shall have become effective and such effectiveness shall not have been terminated or rescinded; (iv) the Purchase Contract Agreement, the Purchase Agreements, the Unit Agreement, the Units, the Warrant Agreement, the Warrants, the Indenture and the Debt Securities are each valid, binding and enforceable agreements of each party thereto (other than as expressly covered above in respect of the Company); and (v) there shall not have occurred any change in law affecting the validity or enforceability of such security. We have also assumed that none of the terms of any security to be established subsequent to the date hereof, the issuance and delivery of such security or the compliance by the Company with the terms of such security will violate any applicable law or public policy or will result in a violation of any provision of any instrument or agreement then binding upon the Company, or any restriction imposed by any court or governmental body having jurisdiction over the Company.

We are members of the Bar of the State of California and the foregoing opinion is limited to the laws of the State of California and the General Corporation Law of the State of Delaware (including the statutory provisions, all applicable provisions of the Delaware Constitution and reported judicial decisions interpreting the foregoing).

We hereby consent to the filing of this opinion as an exhibit to the Registration Statement referred to above and further consent to the reference to our name under the caption "Legal Matters" in the prospectus, which is a part of the Registration Statement. In giving this consent, we do not admit that we are in the category of persons whose consent is required under Section 7 of the Securities Act.

This opinion is rendered solely to you in connection with the above matter. This opinion may not be relied upon by you for any other purpose or relied upon by or furnished to any other person without our prior written consent.

Very truly yours,

/s/ Wilson Sonsini Goodrich & Rosati, P.C.
WILSON SONSINI GOODRICH & ROSATI
Professional Corporation

Consent of Independent Registered Public Accounting Firm

We consent to the reference to our firm under the caption "Experts" in the Registration Statement (Form S-3) and related Prospectus of Denali Therapeutics Inc. for the registration of common stock, preferred stock, debt securities, warrants, purchase contracts, and units and to the incorporation by reference therein of our report dated March 12, 2019, with respect to the consolidated financial statements of Denali Therapeutics Inc. included in its Annual Report (Form 10-K) for the year ended December 31, 2018, filed with the Securities and Exchange Commission.

/s/ Ernst & Young LLP

Redwood City, California

March 12, 2019