
**UNITED STATES
SECURITIES AND EXCHANGE COMMISSION**

Washington, D.C. 20549

FORM 10-Q

(Mark One)

QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the quarterly period ended September 30, 2018
OR

TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the transition period from _____ to _____
Commission File Number: 001-38311

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.)

151 Oyster Point Blvd., 2nd Floor
South San Francisco, CA, 94080
(Address of principal executive offices and zip code)
(650) 866-8548
(Registrant's telephone number, including area code)

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes No

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes No

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a 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. (Check one):

Large accelerated filer	<input type="checkbox"/>	Accelerated filer	<input type="checkbox"/>
Non-accelerated filer	<input checked="" type="checkbox"/>	Smaller reporting company	<input type="checkbox"/>
		Emerging growth company	<input checked="" type="checkbox"/>

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 13(a) of the Exchange Act.

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes No

The number of outstanding shares of the registrant's common stock as of November 2, 2018 was 94,957,092.

TABLE OF CONTENTS

	<u>Page</u>
<u>PART I. FINANCIAL INFORMATION</u>	
Item 1.	<u>3</u>
Financial Statements	
Condensed Consolidated Balance Sheets	<u>3</u>
Condensed Consolidated Statements of Operations and Comprehensive Loss	<u>4</u>
Condensed Consolidated Statements of Cash Flows	<u>5</u>
Notes to Condensed Consolidated Financial Statements (Unaudited)	<u>6</u>
Item 2.	<u>29</u>
Management's Discussion and Analysis of Financial Condition and Results of Operations	
Item 3.	<u>44</u>
Quantitative and Qualitative Disclosures About Market Risk	
Item 4.	<u>45</u>
Controls and Procedures	
<u>PART II. OTHER INFORMATION</u>	
Item 1.	<u>45</u>
Legal Proceedings	
Item 1A.	<u>45</u>
Risk Factors	
Item 2.	<u>100</u>
Unregistered Sales of Equity Securities and Use of Proceeds	
Item 3.	<u>101</u>
Defaults Upon Senior Securities	
Item 4.	<u>101</u>
Mine Safety Disclosures	
Item 5.	<u>102</u>
Other Information	
Item 6.	<u>103</u>
Exhibits	
Signatures	<u>104</u>

PART I. FINANCIAL INFORMATION

ITEM 1. FINANCIAL STATEMENTS

Denali Therapeutics Inc.
Condensed Consolidated Balance Sheets
(Unaudited)
(In thousands, except share amounts)

	September 30, 2018	December 31, 2017
Assets		
Current assets:		
Cash and cash equivalents	\$ 43,651	\$ 218,375
Short-term marketable securities	331,307	187,851
Prepaid expenses and other current assets	8,445	3,381
Total current assets	383,403	409,607
Long-term marketable securities	142,173	60,750
Property and equipment, net	16,245	14,923
Other non-current assets	2,654	1,441
Total assets	\$ 544,475	\$ 486,721
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	\$ 3,354	\$ 2,716
Accrued liabilities	7,393	5,364
Accrued compensation	4,847	5,166
Contract liability	12,658	—
Deferred rent	3,227	855
Other current liabilities	138	63
Total current liabilities	31,617	14,164
Contract liability, less current portion	44,452	—
Deferred rent, less current portion	7,103	6,294
Other non-current liabilities	124	467
Total liabilities	83,296	20,925
Commitments and contingencies (Note 7)		
Stockholders' equity:		
Convertible preferred stock, \$0.01 par value; 40,000,000 shares authorized as of September 30, 2018 and December 31, 2017; 0 shares issued and outstanding as of September 30, 2018 and December 31, 2017	—	—
Common stock, \$0.01 par value; 400,000,000 shares authorized as of September 30, 2018 and December 31, 2017; 93,973,747 shares and 87,480,362 shares issued and outstanding as of September 30, 2018 and December 31, 2017, respectively	1,266	1,201
Additional paid-in capital	766,799	656,660
Accumulated other comprehensive loss	(1,416)	(368)
Accumulated deficit	(305,470)	(191,697)
Total stockholders' equity	461,179	465,796
Total liabilities and stockholders' equity	\$ 544,475	\$ 486,721

See accompanying notes to unaudited condensed consolidated financial statements.

Denali Therapeutics Inc.
Condensed Consolidated Statements of Operations and Comprehensive Loss
(Unaudited)
(In thousands, except share and per share amounts)

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Collaboration revenue	\$ 1,195	\$ —	\$ 3,484	\$ —
Operating expenses:				
Research and development	30,321	18,515	103,274	55,989
General and administrative	8,838	3,773	21,304	10,611
Total operating expenses	39,159	22,288	124,578	66,600
Loss from operations	(37,964)	(22,288)	(121,094)	(66,600)
Interest and other income, net	2,593	444	7,321	1,302
Net loss	(35,371)	(21,844)	(113,773)	(65,298)
Other comprehensive income (loss):				
Net unrealized gain (loss) on marketable securities, net of tax	77	140	(1,048)	136
Comprehensive loss	\$ (35,294)	\$ (21,704)	\$ (114,821)	\$ (65,162)
Net loss per share, basic and diluted	\$ (0.38)	\$ (2.14)	\$ (1.24)	\$ (6.77)
Weighted average number of shares outstanding, basic and diluted	93,665,231	10,231,036	92,056,812	9,643,686

See accompanying notes to unaudited condensed consolidated financial statements.

Denali Therapeutics Inc.
Condensed Consolidated Statements of Cash Flows
(Unaudited)
(In thousands)

	Nine Months Ended September 30,	
	2018	2017
Operating activities		
Net loss	\$ (113,773)	\$ (65,298)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	5,036	2,275
Stock-based compensation expense	13,145	2,952
Net amortization of premiums and discounts on marketable securities	(1,864)	899
Gain (loss) on disposal of property and equipment	(36)	1
Changes in operating assets and liabilities:		
Prepaid expenses and other assets	(5,379)	(3)
Accounts payable	1,235	318
Accrued and other current liabilities	2,639	884
Deferred rent	(1,182)	—
Contract liability	57,110	—
Other non-current liabilities	—	(327)
Net cash used in operating activities	<u>(43,069)</u>	<u>(58,299)</u>
Investing activities		
Purchase of marketable securities	(400,637)	(46,651)
Purchase of property and equipment	(1,956)	(1,804)
Maturities and sales of marketable securities	176,574	102,438
Net cash (used in) provided by investing activities	<u>(226,019)</u>	<u>53,983</u>
Financing activities		
Payments of issuance costs related to issuance for common stock	(1,342)	—
Payments of issuance costs related to issuance for preferred stock	(44)	—
Issuance of common stock in connection with collaboration agreement	94,406	—
Proceeds from exercise of awards under equity incentive plans	2,309	732
Net cash provided by financing activities	<u>95,329</u>	<u>732</u>
Net decrease in cash, cash equivalents and restricted cash	<u>(173,759)</u>	<u>(3,584)</u>
Cash, cash equivalents and restricted cash at beginning of period	218,910	40,388
Cash, cash equivalents and restricted cash at end of period	<u>\$ 45,151</u>	<u>\$ 36,804</u>
Supplemental disclosures of cash flow information		
Tenant improvements provided by the landlord	\$ 4,364	\$ —
Property and equipment purchases accrued but not yet paid	\$ 37	\$ 78
Deferred IPO costs accrued but not yet paid	\$ —	\$ 1,136

See accompanying notes to unaudited condensed consolidated financial statements.

**Denali Therapeutics Inc.
Notes to Condensed Consolidated Financial Statements
(Unaudited)**

1. Significant Accounting Policies

Organization and Description of Business

Denali Therapeutics Inc. ("Denali" or the "Company") is a biopharmaceutical company, incorporated in Delaware, that discovers and develops therapeutics to defeat neurodegenerative diseases. The Company is headquartered in South San Francisco, California.

Basis of Presentation

The accompanying unaudited condensed consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("U.S. GAAP") for interim financial information and the instructions to Form 10-Q and Article 10 of SEC Regulation S-X for interim financial information.

These unaudited condensed consolidated financial statements and notes should be read in conjunction with the audited consolidated financial statements and notes thereto contained in the Annual Report on Form 10-K for the year ended December 31, 2017, as filed with the Securities and Exchange Commission on March 19, 2018 (the "2017 Annual Report on Form 10-K"). The condensed consolidated Balance Sheet as of December 31, 2017 was derived from the audited annual consolidated financial statements as of the period then ended. Certain information and footnote disclosures typically included in the Company's annual consolidated financial statements have been condensed or omitted. The accompanying unaudited condensed consolidated financial statements reflect all adjustments that, in the opinion of management, are necessary for a fair statement of the results of the interim periods presented. All such adjustments are of a normal recurring nature except for the impacts of adopting new accounting standards discussed below. These interim financial results are not necessarily indicative of results expected for the full fiscal year or for any subsequent interim period.

During the three and nine months ended September 30, 2018, except as discussed below in the sections titled Derivatives and Hedging Activities, Revenue Recognition, and Recently Adopted Accounting Standards, there were no material changes to the Company's significant accounting and financial reporting policies from those reflected in the 2017 Annual Report on Form 10-K. For further information with regard to the Company's Significant Accounting Policies, please refer to Note 1, "Significant Accounting Policies," to the Company's Consolidated Financial Statements included in the 2017 Annual Report on Form 10-K.

Initial Public Offering

On December 7, 2017, the Company's Registration Statement on Form S-1 was declared effective by the SEC for Denali's initial public offering ("IPO") of common stock. In connection with the IPO, the Company sold an aggregate of 15,972,221 shares of common stock, including 2,083,333 shares sold pursuant to the underwriters' full exercise of their option to purchase additional shares, at a price to the public of \$18.00 per share. The aggregate net proceeds received by the Company from the offering, net of underwriting discounts and commissions and offering expenses, were \$264.3 million. Upon the closing of the IPO, all then-outstanding shares of Company convertible preferred stock converted into 60,365,020 shares of common stock. The related carrying value of \$378.6 million was reclassified to common stock and additional paid-in capital.

Principles of Consolidation

These unaudited condensed consolidated financial statements include the accounts of the Company and its wholly-owned subsidiary. All intercompany balances and transactions have been eliminated on consolidation. For the Company and its subsidiary, the functional currency has been determined to be U.S. dollars. Monetary assets and liabilities denominated in foreign currency are remeasured at period-end exchange rates. Non-monetary assets and liabilities denominated in foreign currencies are remeasured at historical rates. Foreign currency transaction gains and losses resulting from remeasurement are recognized in interest and other income, net in the condensed consolidated statements of operations and comprehensive loss.

Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires the Company to make certain estimates, judgments and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the condensed consolidated financial statements, as well as the reported amounts of expenses during the reporting period. Actual results could differ from those estimates, and such differences could be material to the condensed consolidated financial position and statements of operations and comprehensive loss.

Concentration of Credit Risk and Other Risks and Uncertainties

Financial instruments that potentially subject the Company to significant concentrations of credit risk consist primarily of cash, cash equivalents, marketable securities and forward foreign currency exchange contracts. Substantially all of the Company's cash and cash equivalents are deposited in accounts with financial institutions that management believes are of high credit quality. Such deposits have and will continue to exceed federally insured limits. The Company maintains its cash with accredited financial institutions and accordingly, such funds are subject to minimal credit risk. The Company has not experienced any losses on its cash deposits.

The Company's investment policy limits investments to certain types of securities issued by the U.S. government, its agencies and institutions with investment-grade credit ratings and places restrictions on maturities and concentration by type and issuer. The Company is exposed to credit risk in the event of a default by the financial institutions holding its cash, cash equivalents and marketable securities and issuers of marketable securities to the extent recorded on the consolidated balance sheets. As of September 30, 2018 and December 31, 2017, the Company had no off-balance sheet concentrations of credit risk.

The Company is exposed to counterparty credit risk on all of its derivative financial instruments. The Company has established and maintains strict counterparty credit guidelines and enters into hedges only with financial institutions that are investment grade or better to minimize the Company's exposure to potential defaults. The Company does not require collateral to be pledged under these agreements.

The Company is subject to a number of risks similar to other early-stage biopharmaceutical companies, including, but not limited to, the need to obtain adequate additional funding, possible failure of current or future preclinical testing or clinical trials, its reliance on third parties to conduct its clinical trials, the need to obtain regulatory and marketing approvals for its product candidates, competitors developing new technological innovations, the need to successfully commercialize and gain market acceptance of the Company's product candidates, its right to develop and commercialize its product candidates pursuant to the terms and conditions of the licenses granted to the Company, protection of proprietary technology, the ability to make milestone, royalty or other payments due under any license or collaboration agreements, and the need to secure and maintain adequate manufacturing arrangements with third parties. If the Company does not successfully commercialize or partner any of its product candidates, it will be unable to generate product revenue or achieve profitability.

Segments

The Company has one operating segment. The Company's chief operating decision maker, its Chief Executive Officer, manages the Company's operations on a consolidated basis for the purposes of allocating resources.

Restricted Cash

The Company's restricted cash consists of the letter of credit for the Company's headquarters building lease, and is included within other non-current assets on the accompanying condensed consolidated balance sheets.

Derivatives and Hedging Activities

The Company accounts for its derivative instruments as either assets or liabilities on the condensed consolidated balance sheet and measures them at fair value. Derivatives are adjusted to fair value through Interest and other income, net in the condensed consolidated statements of operations and comprehensive loss.

Revenue Recognition

License and Collaboration Revenues

The Company analyzes its collaboration arrangements to assess whether they are within the scope of ASC 808, Collaborative Arrangements ("ASC 808") to determine whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities. This assessment is performed throughout the life of the arrangement based on changes in the responsibilities of all parties in the arrangement. For collaboration arrangements within the scope of ASC 808 that contain multiple elements, the Company first determines which elements of the collaboration are deemed to be within the scope of ASC 808 and those that are more reflective of a vendor-customer relationship and, therefore, within the scope of Topic 606. For elements of collaboration arrangements that are accounted for pursuant to ASC 808, an appropriate recognition method is determined and applied consistently, generally by analogy to Topic 606. The accounting treatment pursuant to Topic 606 is outlined below.

The terms of licensing and collaboration agreements entered into typically include payment of one or more of the following: non-refundable, up-front license fees; development, regulatory and commercial milestone payments; payments for manufacturing supply services; and royalties on net sales of licensed products. Each of these payments results in license, collaboration and other revenues, except for revenues from royalties on net sales of licensed products, which are classified as royalty revenues. The core principle of Topic 606 is to recognize revenues when promised goods or services are transferred to customers in an amount that reflects the consideration that is expected to be received in exchange for those goods or services.

In determining the appropriate amount of revenue to be recognized as the Company fulfills its obligations under each of its agreements, the Company performs the following steps: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations based on estimated selling prices; and (v) recognition of revenue when (or as) the Company satisfies each performance obligation.

[Table of Contents](#)

Amounts received prior to satisfying the revenue recognition criteria are recorded as contract liabilities in the Company's consolidated balance sheets. If the related performance obligation is expected to be satisfied within the next twelve months this will be classified in current liabilities. Amounts recognized as revenue prior to receipt are recorded as contract assets in the Company's consolidated balance sheets. If the Company expects to have an unconditional right to receive the consideration in the next twelve months, this will be classified in current assets. A net contract asset or liability is presented for each contract with a customer.

At contract inception, the Company assesses the goods or services promised in a contract with a customer and identifies those distinct goods and services that represent a performance obligation. A promised good or service may not be identified as a performance obligation if it is immaterial in the context of the contract with the customer, if it is not separately identifiable from other promises in the contract (either because it is not capable of being separated or because it is not separable in the context of the contract), or if the performance obligation does not provide the customer with a material right.

The Company considers the terms of the contract and its customary business practices to determine the transaction price. The transaction price is the amount of consideration to which the Company expects to be entitled in exchange for transferring promised goods or services to a customer. The consideration promised in a contract with a customer may include fixed amounts, variable amounts, or both. Variable consideration will only be included in the transaction price when it is not considered constrained, which is when it is probable that a significant reversal in the amount of cumulative revenue recognized will not occur.

If it is determined that multiple performance obligations exist, the transaction price is allocated at the inception of the agreement to all identified performance obligations based on the relative standalone selling prices. The relative selling price for each deliverable is estimated using objective evidence if it is available. If objective evidence is not available, the Company uses its best estimate of the selling price for the deliverable.

Revenue is recognized when, or as, the Company satisfies a performance obligation by transferring a promised good or service to a customer. An asset is transferred when, or as, the customer obtains control of that asset, which for a service is considered to be as the services are received and used. The Company recognizes revenue over time by measuring the progress toward complete satisfaction of the relevant performance obligation using an appropriate input or output method based on the nature of the good or service promised to the customer.

After contract inception, the transaction price is reassessed at every period end and updated for changes such as resolution of uncertain events. Any change in the transaction price is allocated to the performance obligations on the same basis as at contract inception.

Management may be required to exercise considerable judgment in estimating revenue to be recognized. Judgment is required in identifying performance obligations, estimating the transaction price, estimating the stand-alone selling prices of identified performance obligations, which may include forecasted revenues, development timelines, reimbursement rates for personnel costs, discount rates and probabilities of technical and regulatory success, and estimating the progress towards satisfaction of performance obligations.

Net Loss per Share

Basic net loss per share is calculated by dividing the net loss by the weighted-average number of shares of common stock outstanding during the period, without consideration for common stock equivalents. Diluted net loss per share is the same as basic net loss per share, since the effects of potentially dilutive securities are antidilutive given the net loss for each period presented.

Recently Issued Accounting Pronouncements

In February 2016, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update ("ASU") No. 2016-02, *Leases (Topic 842)*, which supersedes the guidance in former ASC 840, *Leases*. The FASB issued further updates to this guidance in July 2018 through ASU 2018-10, *Codification Improvements to Topic 842, Leases* and ASU 2018-11, *Leases (Topic 842): Targeted Improvements*. The new standard requires lessees to apply a dual approach, classifying leases as either finance or operating leases based on the principle of whether or not the lease is effectively a financed purchase by the lessee. This classification will determine whether lease expense is recognized based on an effective interest method or on a straight-line basis over the term of the lease. A lessee is also required to record a right-of-use asset and a lease liability for all leases with a term of greater than 12 months regardless of their classification. Leases with a term of 12 months or less will be accounted for similar to existing guidance for operating leases today. The standard is effective for interim and annual periods beginning after December 15, 2018, with early adoption permitted, and is required to be adopted using a modified retrospective approach. The Company plans to adopt this standard on January 1, 2019. ASU 2016-02 is expected to impact the Company's consolidated financial statements as the Company has certain operating lease arrangements for which the Company is the lessee. Management is continuing to evaluate the impact the adoption of ASU 2016-02 will have on the Company's financial position, results of operations and related disclosures. Management expects that the adoption of this standard will result in the recognition of an asset for the right to use a leased facility on the Company's balance sheet, as well as the recognition of a liability for the lease payments remaining on the lease. While the balance sheet presentation is expected to change, management still does not expect a material change to the condensed consolidated statements of operations and comprehensive loss or cash flows.

In November 2018, the FASB issued ASU No. 2018-18, *Collaborative Arrangements (Topic 808): Clarifying the Interaction between Topic 808 and Topic 606*, which clarifies that certain transactions between collaborative arrangement participants should be accounted for as revenue under Topic 606 when the collaborative arrangement participant is a customer in the context of a unit of account. In those situations, all the guidance in Topic 606 should be applied, including recognition, measurement, presentation, and disclosure requirements. The standard adds unit-of-account guidance in Topic 808 to align with the guidance in Topic 606 (that is, a distinct good or service) when an entity is assessing whether the collaborative arrangement or a part of the arrangement is within the scope of Topic 606, and requires that in a transaction with a collaborative arrangement participant that is not directly related to sales to third parties, presenting the transaction together with revenue recognized under Topic 606 is precluded if the collaborative arrangement participant is not a customer. The standard is effective for interim and annual periods beginning after December 15, 2019, with early adoption permitted, including adoption in any interim period for public business entities for periods in which financial statements have not been issued. Amendments in the standard should be applied retrospectively to the date of initial application of Topic 606, but entities may elect to apply the amendments retrospectively either to all contracts or only to contracts that are not completed at the date of initial application of Topic 606, and should disclose the election. An entity may also elect to apply the practical expedient for contract modifications that is permitted for entities using the modified retrospective transition method in Topic 606. The Company is currently assessing the impact of this standard on its consolidated financial statements.

Recently Adopted Accounting Pronouncements

In May 2014, the FASB issued ASU No. 2014-09, *Revenue from Contracts with Customers (Topic 606)*, which amends the existing accounting standards for revenue recognition. The FASB issued further updates to this guidance through ASU 2016-12 *Narrow-Scope Improvements and Practical Expedients*, ASU 2016-10 *Identifying Performance Obligations and Licensing* and ASU 2016-08 *Principal Versus Agent Considerations (Reporting Revenue Gross Versus Net)*. The new standard is based on principles that govern the recognition of revenue at an amount to which an entity expects to be entitled when products are transferred to customers. This standard was adopted on January 1, 2018 using a full retrospective application. There was no impact to the consolidated financial statements upon adoption of ASU 2014-09 as the Company had not recognized any revenue through December 31, 2017.

[Table of Contents](#)

In November 2016, the FASB issued ASU No. 2016-18, *Statement of Cash Flows (Topic 230): Restricted Cash*. The purpose of ASU 2016-18 is to clarify the guidance for and presentation of restricted cash in the statement of cash flows. The amendment requires beginning-of-period and end-of-period total amounts shown on the statement of cash flows to include cash and cash equivalents as well as restricted cash and restricted cash equivalents. This standard was adopted on January 1, 2018. Accordingly, the condensed consolidated statements of cash flows and Note 3 "Cash and Marketable Securities" have been updated to reconcile cash, cash equivalents and restricted cash for all periods presented.

In May 2017, the FASB issued ASU No. 2017-09, *Compensation - Stock Compensation (Topic 718): Scope of Modification Accounting*, which clarifies when to account for a change to the terms or conditions of a share-based payment award as a modification. Under the new guidance, modification accounting is required only if the fair value, the vesting conditions, or the classification of the award (as equity or liability) changes as a result of the change in terms or conditions. This standard was adopted as of January 1, 2018 and will be applied prospectively to any award modified after the adoption date.

In June 2018, the FASB issued ASU No. 2018-07, *Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting*. ASU 2018-07 is intended to reduce the cost and complexity and to improve financial reporting for non-employee share-based payments. ASU 2018-07 expands the scope of Topic 718, *Compensation-Stock Compensation* (which currently only includes share-based payments to employees) to include share-based payments issued to non-employees for goods or services. Consequently, the accounting for share-based payments to non-employees and employees will be substantially aligned. ASU 2018-07 supersedes Subtopic 505-50, *Equity-Based Payments to Non-Employees*. The Company elected to early adopt this standard effective September 30, 2018. The new guidance will be applied to all new equity-classified share-based payment awards issued to non-employees after the date of adoption. In addition, for all previously issued equity-classified share-based payment awards to non-employees for which a measurement date was not established by the adoption date, these awards were remeasured at fair value as of the adoption date and will no longer be remeasured. The future expense for these share-based payment awards to non-employees will be based on the fair value as of the adoption date. The adoption of this standard will not result in any other changes to the condensed consolidated financial statements.

2. Fair Value Measurements

Assets and liabilities measured at fair value at each balance sheet date are as follows (in thousands):

	September 30, 2018			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash equivalents:				
Money market funds	\$ 27,530	\$ —	\$ —	\$ 27,530
Short-term marketable securities:				
U.S. government treasuries	181,248	—	—	181,248
U.S. government agency securities	—	92,096	—	92,096
Corporate debt securities	—	55,012	—	55,012
Commercial paper	—	2,951	—	2,951
Long-term marketable securities:				
U.S. government treasuries	75,829	—	—	75,829
U.S. government agency securities	—	11,840	—	11,840
Corporate debt securities	—	54,504	—	54,504
Foreign currency derivative contracts	—	4	—	4
Total	\$ 284,607	\$ 216,407	\$ —	\$ 501,014
Liabilities:				
Foreign currency derivative contracts	\$ —	\$ 123	\$ —	\$ 123
Total	\$ —	\$ 123	\$ —	\$ 123

	December 31, 2017			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash equivalents:				
Money market funds	\$ 212,868	\$ —	\$ —	\$ 212,868
Short-term marketable securities:				
U.S. government treasuries	42,587	—	—	42,587
U.S. government agency securities	—	106,139	—	106,139
Corporate debt securities	—	39,125	—	39,125
Long-term marketable securities:				
U.S. government treasuries	39,848	—	—	39,848
U.S. government agency securities	—	19,911	—	19,911
Corporate debt securities	—	991	—	991
Total	\$ 295,303	\$ 166,166	\$ —	\$ 461,469

The carrying amounts of accounts payable and accrued liabilities approximate their fair values due to their short-term maturities.

The Company's Level 2 securities are valued using third-party pricing sources. The pricing services utilize industry standard valuation models, including both income and market-based approaches, for which all significant inputs are observable, either directly or indirectly.

There were no transfers of assets or liabilities between the fair value measurement levels during the three and nine months ended September 30, 2018 or 2017.

3. Cash and Marketable Securities

Cash, cash equivalents and restricted cash

A reconciliation of cash, cash equivalents, and restricted cash reported within the condensed consolidated balance sheets to the amount reported within the condensed consolidated statements of cash flows is shown in the table below (in thousands):

	September 30, 2018	December 31, 2017	September 30, 2017
Cash and cash equivalents	\$ 43,651	\$ 218,375	\$ 36,269
Restricted cash included within prepaid expenses and other current assets	—	84	84
Restricted cash included within other non-current assets	1,500	451	451
Total cash, cash equivalents, and restricted cash	<u>\$ 45,151</u>	<u>\$ 218,910</u>	<u>\$ 36,804</u>

Marketable Securities

All marketable securities were considered available-for-sale at September 30, 2018 and December 31, 2017. The amortized cost, gross unrealized holding gains or losses, and fair value of the Company's marketable securities by major security type at each balance sheet date are summarized in the tables below (in thousands):

	September 30, 2018			Aggregate Fair Value
	Amortized Cost	Unrealized Holding Gains	Unrealized Holding Losses	
Short-term marketable securities:				
U.S. government treasuries	\$ 181,610	\$ —	\$ (362)	\$ 181,248
U.S. government agency securities	92,330	—	(234)	92,096
Corporate debt securities	55,136	—	(124)	55,012
Commercial paper	2,951	—	—	2,951
Total short-term marketable securities	<u>332,027</u>	<u>—</u>	<u>(720)</u>	<u>331,307</u>
Long-term marketable securities:				
U.S. government treasuries	76,226	—	(397)	75,829
U.S. government agency securities	11,919	—	(78)	11,841
Corporate debt securities	54,723	—	(220)	54,503
Total long-term marketable securities	<u>142,868</u>	<u>—</u>	<u>(695)</u>	<u>142,173</u>
Total	<u>\$ 474,895</u>	<u>\$ —</u>	<u>\$ (1,415)</u>	<u>\$ 473,480</u>

	December 31, 2017			
	Amortized Cost	Unrealized Holding Gains	Unrealized Holding Losses	Aggregate Fair Value
Short-term marketable securities:				
U.S. government treasuries	\$ 42,614	\$ —	\$ (27)	\$ 42,587
U.S. government agency securities	106,368	—	(229)	106,139
Corporate debt securities	39,197	—	(72)	39,125
Total short-term marketable securities	188,179	—	(328)	187,851
Long-term marketable securities:				
U.S. government treasuries	39,868	—	(20)	39,848
U.S. government agency securities	19,931	—	(20)	19,911
Corporate debt securities	991	—	—	991
Total long-term marketable securities	60,790	—	(40)	60,750
Total	\$ 248,969	\$ —	\$ (368)	\$ 248,601

As of September 30, 2018 and December 31, 2017, certain of the Company's marketable securities were in an unrealized loss position. The Company determined that it had the ability and intent to hold all marketable securities that have been in a continuous loss position until maturity or recovery, thus there has been no recognition of any other-than-temporary impairment for the three and nine months ended September 30, 2018 and 2017. All marketable securities with unrealized losses as of each balance sheet date have been in a loss position for less than twelve months or the loss is not material.

All of the Company's marketable securities have an effective maturity of less than two years.

4. Derivative Financial Instruments

Foreign Currency Exchange Rate Exposure

The Company uses forward foreign currency exchange contracts to hedge certain operational exposures resulting from potential changes in foreign currency exchange rates. Such exposures result from portions of the Company's forecasted cash flows being denominated in currencies other than the U.S. dollar, primarily the Euro and British Pound. The derivative instruments the Company uses to hedge this exposure are not designated as cash flow hedges, and as a result, changes in their fair value are recorded in Interest and other income, net, on the Company's condensed consolidated statements of operations and comprehensive loss.

The fair values of forward foreign currency exchange contracts are estimated using current exchange rates and interest rates and take into consideration the current creditworthiness of the counterparties. Information regarding the specific instruments used by the Company to hedge its exposure to foreign currency exchange rate fluctuations is provided below. The Company did not have foreign currency exchange contracts prior to June 2018.

The following table summarizes the Company's forward foreign currency exchange contracts outstanding as of September 30, 2018 (notional amounts in thousands):

Foreign Exchange Contracts	Number of Contracts	Aggregate Notional ⁽¹⁾ Amount in Foreign Currency	Maturity
Euros	24	3,884	Oct. 2018 - Aug. 2019
British Pounds	19	1,625	Oct. 2018 - Aug. 2019
Swiss Francs	16	466	Oct. 2018 - Aug. 2019
Total	59		

⁽¹⁾The notional amount represents the net amount of foreign currency that will be received upon maturity of the forward contracts.

[Table of Contents](#)

The maximum length of time over which the Company is hedging its exposure to changes in exchange rates is through August 2019.

The derivative liability balance of \$0.1 million is recorded in Other current liabilities and the derivative asset balance of \$3,667 is recorded in Prepaid assets and other current assets on the condensed consolidated balance sheet as of September 30, 2018. The net loss associated with the Company's derivative instruments of \$0.1 million is recognized in Interest and other income, net on the condensed consolidated statement of operations and comprehensive loss for the three and nine months ended September 30, 2018.

5. Acquisition

In August 2016, the Company entered into a License and Collaboration Agreement ("F-star Collaboration Agreement") with F-star Gamma Limited ("F-star Gamma"), F-star Biotechnologische Forschungs-Und Entwicklungsges M.B.H ("F-star GmbH") and F-star Biotechnology Limited ("F-Star Ltd") (collectively, "F-star") to leverage F-star's modular antibody technology and the Company's expertise in the development of therapies for neurodegenerative diseases. In connection with the entry into the F-star Collaboration Agreement, the Company also purchased an option for an upfront option fee of \$0.5 million (the "buy-out-option"), to acquire all of the outstanding shares of F-star Gamma pursuant to a pre-negotiated buy-out option agreement (the "Option Agreement").

On May 30, 2018, the Company exercised such buy-out option and entered into a Share Purchase Agreement (the "Purchase Agreement") with the shareholders of F-star Gamma and Shareholder Representative Services LLC, pursuant to which the Company acquired all of the outstanding shares of F-star Gamma (the "Acquisition").

As a result of the Acquisition, F-star Gamma has become a wholly-owned subsidiary of the Company and the Company has changed the entity's name to Denali BBB Holding Limited. In addition, the Company became a direct licensee of certain intellectual property of F-star Ltd (by way of the Company's assumption of F-star Gamma's license agreement with F-star Ltd, dated August 24, 2016, (the "F-star Gamma License")). The Company has made initial exercise payments under the Purchase Agreement and the F-star Gamma License in the aggregate, of \$18.0 million, less the estimated net liabilities of F-star Gamma, which is approximately \$0.2 million. In addition, the Company is required to make future contingent payments, to F-star Ltd and the former shareholders of F-star Gamma, up to a maximum amount of \$447.0 million in the aggregate upon the achievement of certain defined preclinical, clinical, regulatory and commercial milestones. The amount of the contingent payments varies based on whether F-star delivers an Fcab (constant Fc-domains with antigen-binding activity) that meets pre-defined criteria and whether the Fcab has been identified solely by the Company or solely by F-star or jointly by the Company and F-star.

Under the terms of the original F-star Collaboration Agreement, the Company could nominate up to three Fcab targets ("Accepted Fcab Targets") within the first three years of the date of the F-star Collaboration Agreement. Upon entering into the F-star Collaboration Agreement, the Company had selected transferrin receptor ("TfR") as the first Accepted Fcab Target and paid F-star Gamma an upfront fee of \$5.5 million, which included selection of the first Accepted Fcab Target. In May 2018, the Company exercised its right to nominate two additional Fcab Targets and identified a second Accepted fcab Target. The Company is obligated to make a one-time payment for the two additional Accepted Fcab Targets of, in the aggregate, \$6.0 million and has extended the time period for its selection of the third Accepted Fcab Target until approximately the fourth anniversary of the date of the original F-Star Collaboration Agreement.

The Company is also responsible for certain research costs incurred by F-star Ltd in conducting activities under each agreed development plan, for up to 24 months. These research costs for the agreed TfR development plan will be up to \$2.1 million.

[Table of Contents](#)

The Company concluded that the assets acquired and liabilities assumed upon the exercise of the Option Agreement did not meet the accounting definition of a business, and as such, the acquisition was accounted for as an asset purchase. The Company recorded the upfront purchase price less estimated net liabilities acquired of \$17.8 million in research and development expense in the accompanying condensed consolidated statement of operations and comprehensive loss in the nine months ended September 30, 2018 since it represented consideration for in-process research and development with no future alternative use. The upfront option fee of \$0.5 million previously included within other non-current assets was also included in research and development expense during the nine months ended September 30, 2018.

As this transaction was accounted for as an asset purchase rather than a business combination, no amounts were recognized on the acquisition date relating to the contingent consideration. Contingent consideration will be recognized in research and development expense as incurred.

The Company recognized \$0.3 million and \$0.8 million of research and development expense related to the funding of F-star Gamma research costs during the three and nine months ended September 30, 2018, respectively, and \$0.3 million and \$0.8 million during the three and nine months ended September 30, 2017, respectively.

6. License and Collaboration Agreements

Takeda

On January 3, 2018, the Company entered into a Collaboration and Option Agreement ("Takeda Collaboration Agreement") with Takeda Pharmaceutical Company Limited ("Takeda"), pursuant to which the Company granted Takeda an option in respect of three programs to develop and commercialize, jointly with the Company, certain biologic products that are enabled by Denali's BBB delivery technology and intended for the treatment of neurodegenerative disorders. The three programs are Denali's ATV:BACE1/Tau and ATV: TREM2 programs, as well as a third identified discovery stage program. The Takeda Collaboration Agreement became effective on February 12, 2018 when the requirements of the Hart-Scott-Rodino Antitrust Improvements Act of 1976 were satisfied.

Under the Takeda Collaboration Agreement and unless otherwise agreed jointly between both parties, Denali will be responsible, at its cost, for conducting activities relating to pre-IND development of biologic products directed to the three identified targets and enabled by its BBB delivery technology targeting transferrin receptor during the applicable research period. The period through which the option can be exercised continues for each target until the first biologic product directed to the relevant target is IND-ready or about five years after selection of the target, whichever is earlier.

The Takeda Collaboration Agreement provided that Takeda pay a \$40.0 million upfront payment, and up to an aggregate of \$25.0 million with respect to each program directed to a target and based upon the achievement of certain preclinical milestone events, up to \$75.0 million in total. The upfront payment of \$40.0 million was received in February 2018, as well as the first preclinical milestone payment of \$5.0 million related to one of the programs.

If Takeda exercises its option with respect to a particular target, then Takeda will have the right to develop and commercialize, jointly with the Company, a specified number of biologic products enabled by its BBB delivery technology that were developed during the research period and which are directed to the relevant target, and the Company will grant to Takeda a co-exclusive license under the intellectual property the Company controls related to those biologic products.

Takeda is obligated to pay Denali a \$5.0 million option fee for each target for which Takeda exercises its option, up to \$15.0 million in total.

[Table of Contents](#)

In addition, Takeda may be obligated to pay Denali up to an aggregate of \$707.5 million upon achievement of certain clinical and regulatory milestone events if Takeda exercises its option for all three collaboration programs. Takeda may also be obligated to pay Denali up to \$75.0 million per biologic product upon achievement of a certain sales-based milestone, or an aggregate of \$225.0 million if one biologic product from each program achieves the milestone.

If Takeda exercises its option for a particular target, Denali and Takeda will share equally the development and commercialization costs, and, if applicable, the profits, for each collaboration program. However, for each collaboration program, the Company may elect not to continue sharing development and commercialization costs, or Takeda may elect to terminate Denali's cost-profit sharing rights and obligations if, following notice from Takeda and a cure period, the Company fails to satisfy its cost sharing obligations with respect to the relevant collaboration program. After such an election by the Company or termination by Takeda becomes effective, Denali will no longer be obligated to share in the development and commercialization costs for the relevant collaboration program, and will not share in any profits from that collaboration program. Instead the Company will be entitled to receive tiered royalties. The royalty rates will be in the low- to mid-teen percentages on net sales, or low- to high-teen percentages on net sales if certain co-funding thresholds have been met at the time of the Company's election to opt out of co-development or Takeda's termination of Denali's cost-profit sharing rights and obligations, and, in each case, these royalty rates will be subject to certain reductions specified in the Takeda Collaboration Agreement. Takeda will pay these royalties for each biologic product included in the relevant collaboration program, on a country-by-country basis, until the latest of (i) the expiration of certain patents covering the relevant biologic product, (ii) the expiration of all regulatory exclusivity for that biologic product, and (iii) an agreed period of time after the first commercial sale of that biologic product in the applicable country, unless biosimilar competition in excess of a significant level specified in the Takeda Collaboration Agreement occurs earlier, in which case Takeda's royalty obligations in the applicable country would terminate.

For each collaboration program for which costs and profits are shared with Takeda, Denali will lead the conduct of clinical activities for each indication through the first Phase 2 trial with a clinical outcomes-based efficacy endpoints, and Takeda will lead the conduct of all subsequent clinical activities for that indication. Further, Denali and Takeda will jointly commercialize biologic products included in the relevant collaboration program in the United States and China. Unless Denali has opted out of cost-sharing for two collaboration programs, it has the right to lead commercialization activities in the United States for one collaboration program and Takeda will lead commercialization activities in the United States for all collaboration programs for which Denali does not lead commercialization activities. Further, Takeda will lead commercialization activities in China and will solely conduct commercialization activities in all other countries. The Company has the right to lead all manufacturing activities for all collaboration programs for which the parties are sharing costs and profits.

Each party may terminate the Takeda Collaboration Agreement in its entirety, or with respect to a particular collaboration program, as applicable, if the other party remains in material breach of the Takeda Collaboration Agreement following a cure period to remedy the material breach. Takeda may terminate the Takeda Collaboration Agreement in its entirety or with respect to any particular collaboration program, for convenience and after giving a specified amount of prior notice, but Takeda may not do so for a certain period of time after the Effective Date of the Takeda Collaboration Agreement. Takeda may also terminate the Takeda Collaboration Agreement with respect to any collaboration program if the joint steering committee ("JSC") established under the Takeda Collaboration Agreement unanimously agrees that a material safety event has occurred with respect to the applicable collaboration program. Denali may terminate the Takeda Collaboration Agreement with respect to a particular collaboration program if Takeda fails to conduct material development and commercial activities for a specified period of time with respect to a collaboration program, unless Takeda cures such failure within a certain period of time. Denali and Takeda may each terminate the Takeda Collaboration Agreement in its entirety if the other party is declared insolvent or in similar financial distress or if, subject to a specified cure period, the other party challenges any patents licensed to it under the Takeda Collaboration Agreement.

[Table of Contents](#)

Pursuant to the terms of the Takeda Collaboration Agreement, the Company entered into a common stock purchase agreement (the "Stock Purchase Agreement") with Takeda on January 3, 2018, pursuant to which Takeda purchased 4,214,559 shares of Denali's common stock (the "Shares") for an aggregate purchase price of \$110.0 million. The sale of the Shares closed on February 23, 2018. The fair market value of the common stock sold to Takeda was \$94.4 million, based on the closing stock price of \$22.40 on the date of issuance, resulting in a \$15.6 million premium paid to the Company above the fair value of the Company's common stock which was credited to contract liability in our condensed consolidated balance sheet.

The Company believes that the Takeda Collaboration Agreement is a collaboration arrangement as defined in ASC 808, *Collaborative Agreements*. Further, during the research period, the Company believes that the arrangement is a contract with a customer as defined in ASC 606, *Revenue From Contracts With Customers*. The Takeda Collaboration Agreement and the Stock Purchase Agreement are being accounted for as one arrangement because they were entered into at the same time with interrelated financial terms.

The Company identified performance obligations during the research period consisting of the license, the development options, and JSC participation together with the research services for each collaboration program. The license rights, JSC involvement, option and research services are considered to be a single performance obligation for each program since the research services are highly interrelated with the option and JSC involvement and will significantly modify the license. The performance obligations under each of the three programs are separate since the activities and risks under the programs are distinct.

The Company has determined that all other goods or services which are contingent upon Takeda exercising its option for each program are not considered performance obligations at the inception of the arrangement.

The transaction price at inception included fixed consideration consisting of the upfront fee of \$40.0 million, the \$15.6 million premium on the sale of common stock, and the first preclinical milestone payment of \$5.0 million. It also included variable consideration of \$26.0 million relating to future milestones that are not constrained. The amount of variable consideration was estimated using the most likely amount method. In October 2018, the Company confirmed the first preclinical milestone was met for the third identified discovery stage program, triggering a milestone payment of \$5.0 million, which is expected to be received in November 2018.

The remaining \$44.0 million of preclinical milestones were considered constrained at the inception of the arrangement since the Company could not conclude it is probable that a significant reversal in the amount recognized will not occur. Additionally, cost and profit sharing income, and the development and commercial milestones as outlined above, have not been considered given Takeda has not exercised its options for the development and commercial phases for each program. There was no change in the transaction price from inception through September 30, 2018. This will be reassessed at each reporting period.

The transaction price has been ascribed in its entirety to the three performance obligations identified in the research term of the Takeda Collaboration Agreement.

Revenue is recognized when, or as, the Company satisfies its performance obligations by transferring the promised services to Takeda. Revenue will be recognized over time using the input method, based on costs incurred to perform the research services, since the level of costs incurred over time is thought to best reflect the transfer of services to Takeda.

A contract liability of \$57.1 million is recorded on the balance sheet at September 30, 2018, which relates to the three performance obligations identified, with such amounts to be recognized over the period of the pre-IND research services, which is expected to be several years.

[Table of Contents](#)

Revenue recognized relating to future milestone payments of approximately \$1.2 million, for which the Company concluded that it is probable that a significant reversal in the amount recognized will not occur, is presented net of contract liability on the balance sheet.

Significant changes in the net contract liability balance during the period are as follows (in thousands):

	Contract liability
Balance at January 1, 2018	\$ —
Increases due to cash received, excluding amounts recognized as revenue during the period	58,329
Decreases due to revenue recognized in the period for which cash has not been received	(1,219)
Balance at September 30, 2018	<u>\$ 57,110</u>

There are no receivables or net contract assets as of September 30, 2018 associated with this arrangement.

In assessing this arrangement, management was required to exercise considerable judgment in estimating revenue to be recognized. Management applied judgment in determining the separate performance obligations in the research period, estimating variable consideration, and estimating total future costs when using the input method.

Genentech

In June 2016, the Company entered into an Exclusive License Agreement with Genentech, Inc. ("Genentech"). The agreement gives the Company access to Genentech's LRRK2 small molecule program for Parkinson's disease. Under the agreement, Genentech granted the Company (i) an exclusive, worldwide, sublicenseable license under Genentech's rights to certain patents and patent applications directed to small molecule compounds which bind to and inhibit LRRK2 and (ii) a non-exclusive, worldwide, sublicenseable license to certain related know-how, in each case, to develop and commercialize certain compounds and licensed products incorporating any such compound. The Company is obligated to use commercially reasonable efforts during the first three years of the agreement to research, develop and commercialize at least one licensed product.

As consideration, the Company paid an upfront fee of \$8.5 million and a technology transfer fee of \$1.5 million, both of which were recognized as research and development expense for the year ended December 31, 2016.

The Company may owe Genentech milestone payments upon the achievement of certain development, regulatory, and commercial milestones, up to a maximum of \$315.0 million in the aggregate, as well as royalties on net sales of licensed products ranging from low to high single-digit percentages, with the exact royalty rate dependent on various factors, including (i) whether the compound incorporated in the relevant licensed product is a Genentech-provided compound or a compound acquired or developed by the Company, (ii) the date a compound was first discovered, derived or optimized by the Company, (iii) the existence of patent rights covering the relevant licensed product in the relevant country, (iv) the existence of orphan drug exclusivity covering a licensed product that is a Genentech-provided compound and (v) the level of annual net sales of the relevant licensed product. The Company also has the right to credit a certain amount of third-party royalty and milestone payments against royalty and milestone payments owed to Genentech, up to a maximum reduction of fifty percent. The Company's royalty payment obligations will expire on a country-by-country and licensed product-by-licensed product basis upon the later of (a) ten years after the first commercial sale of such licensed product in such country and (b) the expiration of the last valid claim of a licensed patent covering such licensed product in such country.

[Table of Contents](#)

Genentech may terminate the agreement if the Company challenges any of the patent rights licensed to the Company by Genentech, or if the Company materially breaches the agreement, subject to specified notice and cure provisions, or enters into bankruptcy or insolvency proceedings. If Genentech terminates the agreement for the Company's material breach, bankruptcy or insolvency after the Company has made a milestone payment to Genentech, then the Company is obligated to grant to Genentech an exclusive right of first negotiation with respect to certain of the Company's patents, know-how and regulatory filings directed to Genentech-provided compounds. The Company does not have the right to terminate the agreement without cause, but may terminate the agreement for Genentech's material breach, subject to specified notice and cure provisions.

Unless earlier terminated, the agreement with Genentech will continue in effect until all of the Company's royalty and milestone payment obligations to Genentech expire. Following expiration of the agreement, the Company will retain the licenses under the intellectual property Genentech licensed to the Company on a non-exclusive, royalty-free basis.

The first clinical milestone of \$2.5 million became due in June 2017 upon first patient dosing in the Phase 1 clinical trial for DNL201. The full amount was recorded as research and development expense in the nine months ended September 30, 2017.

7. Commitments and Contingencies

Lease Obligations

In September 2015, the Company entered into a non-cancelable operating lease for its corporate headquarters comprising 38,109 of rentable square feet in a building in South San Francisco (the "Headquarters Lease"). The Headquarters Lease commenced on August 1, 2016 with a lease term of eight years. The Headquarters Lease provides for monthly base rent amounts escalating over the term of the lease. In addition, the Headquarters Lease provided a tenant improvement allowance ("TIA") of up to \$7.4 million, of which \$1.9 million was to be repaid to the landlord in the form of additional monthly rent with interest applied. This additional monthly rent commenced in November 2016 when the entire TIA was utilized, and resulted in an increase of base rent of \$0.4 million per year over the eight-year lease term.

On May 2, 2018, the Company entered into an amendment to the Headquarters Lease (the "Headquarters Lease Amendment") to relocate and expand its headquarters to 148,020 rentable square feet in a to-be-constructed building located in South San Francisco, California (the "New Premises"). The Headquarters Lease Amendment has a contractual term of ten years from the legal commencement date, which is the later of February 1, 2019 or the date that the premises are ready for occupancy. For accounting purposes, the lease commencement date was determined to be August 1, 2018, which was the date at which the Company obtained control over the property. The Company has an option to extend the lease term for a period of ten years by giving the landlord written notice of the election to exercise the option at least nine months, but not more than twelve months, prior to the expiration of the Headquarters Lease Amendment lease term.

Under the terms of the Headquarters Lease, the Company was required to pay a security deposit of \$0.5 million, which was increased to \$1.5 million under the Headquarters Lease Amendment. This is recorded as other non-current assets in the accompanying condensed consolidated balance sheets.

The Headquarters Lease Amendment provides for monthly base rent amounts escalating over the term of the lease. In addition, the Headquarters Lease Amendment provides a TIA of up to \$25.9 million, of which \$4.4 million, if utilized, would be repaid to the landlord in the form of additional monthly rent. The Company will also be required to pay its share of operating expenses for the New Premises.

[Table of Contents](#)

The total \$7.4 million TIA under the 2015 Headquarters Lease was recorded as leasehold improvements and deferred rent liability on the condensed consolidated balance sheet under the Headquarters Lease. The Company is amortizing the deferred rent liability as a reduction of rent expense and the leasehold improvement through an increase of depreciation expense of leasehold improvements ratably over the remaining period of expected use.

The portion of the TIA utilized to date under the Headquarters Lease Amendment was \$4.4 million and has been recorded as leasehold improvements and deferred rent liability on the condensed consolidated balance sheet as of September 30, 2018. The Company will amortize the deferred rent liability as a reduction of rent expense and the leasehold improvement through an increase of depreciation expense of leasehold improvements ratably over the period of expected use, which is expected to commence in April 2019.

The Company recognizes rent expense on a straight-line basis over the non-cancelable lease term and records the difference between cash rent payments and the recognition of rent expense as a deferred rent liability. Where leases contain escalation clauses, rent abatements, and/or concessions such as rent holidays and landlord or tenant incentives or allowances, the Company applies them in the determination of straight-line rent expense over the lease term. The Company records tenant improvement allowances as deferred rent and associated expenditures as leasehold improvements that are being amortized over the shorter of their estimated useful life or the term of the lease. The Company does not assume renewals in its determination of the lease term unless the renewals are deemed by management to be reasonably assured at lease inception.

As of September 30, 2018, the future minimum lease payments under the Headquarters Lease and subsequently the Headquarters Lease Amendment are as follows (in thousands):

Year Ended December 31:

2018 (three months)	\$	658
2019		4,941
2020		9,097
2021		9,716
2022		10,056
2023 and later		71,290
	\$	<u>105,758</u>

Rent expense excluding amortization of leasehold improvements was \$2.4 million and \$3.7 million for the three and nine months ended September 30, 2018, and \$0.4 million and \$1.6 million for the three and nine months ended September 30, 2017, respectively.

Indemnification

In the ordinary course of business, the Company may provide indemnifications of varying scope and terms to vendors, lessors, business partners, board members, officers, and other parties with respect to certain matters, including, but not limited to, losses arising out of breach of such agreements, services to be provided by the Company, negligence or willful misconduct of the Company, violations of law by the Company, or from intellectual property infringement claims made by third parties. In addition, the Company has entered into indemnification agreements with directors and certain officers and employees that will require the Company, among other things, to indemnify them against certain liabilities that may arise by reason of their status or service as directors, officers or employees. No demands have been made upon the Company to provide indemnification under such agreements, and thus, there are no claims that the Company is aware of that could have a material effect on the Company's balance sheet, statements of comprehensive loss, or statements of cash flows.

Commitments

Effective September 2017, the Company entered into a Development and Manufacturing Services Agreement as amended (“DMSA”) with Lonza Sales AG (“Lonza”) for the development and manufacture of biologic products. Under the DMSA, the Company will execute purchase orders based on project plans authorizing Lonza to provide development and manufacturing services with respect to certain of the Company’s antibody and enzyme products, and will pay for the services provided and batches delivered in accordance with the DMSA and project plan. Unless earlier terminated, the Lonza agreement will expire on September 6, 2022.

As of September 30, 2018, the Company had several purchase orders for biological product development and manufacturing costs totaling \$13.0 million. The activities under these purchase orders are expected to be completed by April 2024. During the three and nine months ended September 30, 2018, the Company incurred costs of \$1.4 million and \$2.6 million, respectively, and made payments of \$1.3 million and \$2.0 million, respectively, for the development and manufacturing services rendered under the agreement. As of September 30, 2018, the Company had total non-refundable purchase commitments of \$7.7 million under the DMSA.

8. Stock-Based Awards

2017 Equity Incentive Plan

In December 2017, the Company adopted the 2017 Equity Incentive Plan (the “2017 Plan”), which initially reserved 6,379,238 shares for the issuance of stock options, restricted stock and other stock awards, to employees, non-employee directors, and consultants under terms and provisions established by the Board of Directors and approved by the stockholders. Awards granted under the 2017 Plan expire no later than ten years from the date of grant. For stock options, the option price shall not be less than 100% of the estimated fair value on the day of grant. Options granted typically vest over a four-year period but may be granted with different vesting terms.

2015 Stock Incentive Plan

In May 2015, the Company adopted the 2015 Stock Incentive Plan (the “2015 Plan”), which as amended, reserved 8,325,000 shares for the issuance of stock options, restricted stock and other stock awards, to employees, non-employee directors, and consultants under terms and provisions established by the Board of Directors and approved by the stockholders. Awards granted under the 2015 Plan expire no later than ten years from the date of grant. For stock options, the option price shall not be less than 100% of the estimated fair value on the day of grant. For all stock options granted between August 2015 and February 2016 with an exercise price of \$0.68, a deemed fair value of \$1.20 per share was used in calculating stock-based compensation expense, which was determined using management hindsight. Options granted typically vest over a four-year period but may be granted with different vesting terms.

Upon adoption of the 2017 Plan, no new awards or grants are permitted under the 2015 Plan, and the 169,238 shares that were then unissued and available for future award under the 2015 Plan became available under the 2017 Plan. The 2015 Plan will continue to govern restricted stock awards and option awards previously granted thereunder.

As of September 30, 2018, there were 2,659,306 shares available for the Company to grant under the 2017 Plan.

Stock Option Activity

The following table summarizes option award activity under the 2017 Plan and the 2015 Plan:

	Number of Options	Weighted- Average Exercise Price	Weighted- Average remaining contractual life (years)	Aggregate Intrinsic Value (in thousands)
Balance at December 31, 2017	6,689,479	\$ 4.08	8.37	\$ 77,317
Options granted	3,591,734	20.55		
Options exercised	(489,483)	2.57		
Options forfeited	(238,542)	10.36		
Balance at September 30, 2018	<u>9,553,188</u>	\$ 10.18	8.39	\$ 110,407
Options vested and expected to vest at September 30, 2018	<u>7,808,456</u>	\$ 12.31	8.72	\$ 73,663
Options exercisable at September 30, 2018	<u>1,779,017</u>	\$ 3.78	7.84	\$ 31,946

Aggregate intrinsic value represents the difference between the Company's fair value of its common stock and the exercise price of outstanding options. The total intrinsic value of options exercised was \$2.6 million and \$7.3 million for the three and nine months ended September 30, 2018, and \$1.2 million and \$3.5 million for the three and nine months ended September 30, 2017, respectively. During the three and nine months ended September 30, 2018, the weighted-average grant-date fair value of the vested options was \$4.01 and \$3.29 per share, respectively. During the three and nine months ended September 30, 2017, the weighted-average grant-date fair value of the vested options was \$2.43 and \$2.08 per share, respectively. The weighted-average grant date fair value of all options granted during the three and nine months ended September 30, 2018 was \$11.01 and \$15.05 per share, respectively. The weighted-average grant date fair value of all options granted during the three and nine months ended September 30, 2017 was \$7.08 and \$4.84 per share, respectively.

Stock Options Granted to Employees with Service-Based Vesting

The estimated fair value of stock options granted to employees were calculated using the Black-Scholes option-pricing model using the following assumptions:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Expected term (in years)	6.08	6.08	5.50 - 6.08	6.08
Volatility	81.9% - 84.8%	86.8% - 88.1%	80.0% - 87.5%	86.8% - 91.3%
Risk-free interest rate	2.8% - 2.9%	1.8% - 1.9%	2.6% - 2.9%	1.8% - 2.3%
Dividend yield	—	—	—	—

Expected Term: The expected term represents the period that the options granted are expected to be outstanding and is determined using the simplified method (based on the mid-point between the vesting date and the end of the contractual term).

Expected Volatility: The Company uses an average historical stock price volatility of comparable public companies within the biotechnology and pharmaceutical industry that were deemed to be representative of future stock price trends as the Company does not have sufficient trading history for its common stock. The Company will continue to apply this process until a sufficient amount of historical information regarding the volatility of its own stock price becomes available.

Risk-Free Interest Rate: The Company based the risk-free interest rate over the expected term of the options based on the constant maturity rate of U.S. Treasury securities with similar maturities as of the date of the grant.

[Table of Contents](#)

Expected Dividend: The Company has not paid and does not anticipate paying any dividends in the near future. Therefore, the expected dividend yield was zero.

Early Exercise of Stock Options

The Company permits early exercise of certain stock options prior to vesting by certain directors and officers. Any shares issued pursuant to unvested options are restricted and subject to repurchase by the Company until the conditions for vesting are met. The amounts paid for shares purchased under an early exercise of stock options and subject to repurchase by the Company are reported in stockholders' equity once those shares vest. Upon termination of employment of an option holder, the Company has the right to repurchase, at the original purchase price, any unvested restricted shares.

A total of \$31,874 and \$0.4 million was reclassified from other non-current liabilities to stockholders' equity during the three and nine months ended September 30, 2018, respectively, related to vesting of early exercised options. A total of \$31,874 and \$0.2 million was reclassified from other non-current liabilities to stockholders' equity during the three and nine months ended September 30, 2017, respectively, related to vesting of early exercised options. Unvested early exercised options of \$0.1 million and \$0.5 million remained in other non-current liabilities as of September 30, 2018 and December 31, 2017, respectively.

Performance and Market Contingent Stock Options Granted to Employees

In August and November 2015, the Board of Directors granted performance- and market- contingent options to purchase 1,619,738 shares and 125,000 shares of the Company's common stock, respectively, to members of the senior management team. These awards have an exercise price of \$0.68 per share.

These awards have two separate market triggers for vesting based upon either (i) the successful achievement of stepped target closing prices on a national securities exchange for 90 consecutive trading days later than 180 days after the Company's initial public offering for its common stock, or (ii) stepped target prices for a change in control transaction. By definition, the market condition in these awards can only be achieved after the performance condition of a liquidity event has been achieved. As such, the requisite service period is based on the estimated period over which the market condition can be achieved. When a performance goal is deemed to be probable of achievement, time-based vesting and recognition of stock-based compensation expense commences. In the event any the milestones are not achieved by the specified timelines, such award will terminate and no longer be exercisable with respect to that portion of the shares. The maximum potential expense associated with the performance- and market- contingent awards is \$6.2 million (\$5.8 million and \$0.4 million of general and administrative and research and development expense, respectively) if all of the performance and market conditions are achieved as stated in the option agreement. Management evaluates whether the achievement of performance- and market- contingent awards is probable at each reporting date. Management has concluded that the achievement of these awards is not probable through September 30, 2018. Accordingly, no stock-based compensation expense has been recognized in the three and nine months ended September 30, 2018 and 2017 related to these awards.

The Company uses a lattice model with a Monte Carlo simulation to value stock options with performance and market conditions. This valuation methodology utilizes the estimated fair value of the Company's common stock on grant date and several key assumptions, including expected volatility of the Company's stock price based on comparable public companies, risk-free rates of return and expected dividend yield.

Stock Options Granted to Non-Employees with Service-Based Vesting Valuation Assumptions

Stock-based compensation related to stock options granted to non-employees is recognized as the stock options are earned. Prior to the adoption of ASU 2018-07 during the third quarter of 2018, the unvested options granted to non-employees were revalued using the Company's estimate of fair value on each reporting date. Subsequent to the adoption of ASU 2018-07, existing stock options granted to non-employees will no longer be revalued, and the estimated fair value of new stock options granted to non-employees will be calculated on the date of grant and not remeasured, similar to stock options granted to employees.

The estimated fair value of the stock options granted to non-employees has been calculated using the Black-Scholes option-pricing model with the following assumptions:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Expected term (in years)	7.14 - 9.36	7.75 - 8.35	7.14 - 9.86	7.75 - 9.45
Volatility	89.4% - 90.5%	86.8% - 90.5%	88.9% - 103.1%	86.8% - 98.0%
Risk-free interest rate	3.0%	2.2%	2.7% - 3.0%	2.2% - 2.4%
Dividend yield	—	—	—	—

Restricted Stock Activity

Under the 2017 Plan, the Company may grant restricted stock awards ("RSAs"), which represent restricted shares of common stock issued upon the date of grant in which the recipient's rights in the stock are restricted until the shares are vested, and restricted stock units ("RSUs"), which represent a commitment to issue shares of common stock in the future upon vesting. The fair value of restricted stock underlying the RSAs and RSUs is determined based on the closing price of the Company's common stock on the date of grant.

Aggregated information regarding RSAs and RSUs granted under the Plan for the nine months ended September 30, 2018 is summarized below:

	Share Awards & Units	Weighted-Average Fair Value at Date of Grant per Share
Unvested at December 31, 2017	2,293,788	\$ 0.18
Granted	149,658	15.92
Vested	(1,532,994)	0.18
Forfeited	—	—
Unvested at September 30, 2018	910,452	\$ 2.76
Vested and expected to vest—September 30, 2018	910,452	\$ 2.76

At September 30, 2018, there was \$2.4 million of total unrecognized compensation cost related to unvested RSAs and RSUs, all of which is expected to be recognized over a remaining weighted-average vesting period of 0.7 years.

Employee Stock Purchase Plan

In December 2017, the Company adopted the 2017 Employee Stock Purchase Plan (the "2017 ESPP"), which initially reserved 1,000,000 shares of the Company's common stock for employee purchases under terms and provisions established by the Board of Directors. Under the 2017 ESPP, employees may purchase common stock through payroll deductions at a price equal to 85% of the lower of the fair market value of common stock on the first trading day of each offering period or on the exercise date. The 2017 ESPP provides for consecutive, overlapping 12-month offering periods. The offering periods are scheduled to start on the first trading day on or after May 31 or November 30 of each year, except for the first offering period which commenced on December 8, 2017, the first trading day after the effective date of the Company's registration statement. Contributions under the 2017 ESPP are limited to a maximum of 15% of an employee's eligible compensation.

The estimated fair value of stock purchase rights granted under the ESPP were calculated using the Black-Scholes option-pricing model using the following assumptions:

	Nine Months Ended September 30, 2018
Expected term (in years)	0.50 - 1.00
Volatility	63.2% - 63.7%
Risk-free interest rate	2.1%
Dividend yield	—

The Company did not issue any new stock purchase rights under the 2017 ESPP during the three months ended September 30, 2018.

Stock-Based Compensation Expense

The Company's results of operations include expenses relating to stock-based compensation as follows (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Research and development	\$ 2,907	\$ 725	\$ 7,179	\$ 1,947
General and administrative	2,603	403	5,966	1,005
Total	<u>\$ 5,510</u>	<u>\$ 1,128</u>	<u>\$ 13,145</u>	<u>\$ 2,952</u>

As of September 30, 2018 and December 31, 2017, total unamortized stock-based compensation expense related to unvested stock-based awards that are expected to vest was \$60.2 million and \$17.7 million, respectively. The weighted-average periods over which such stock-based compensation expense will be recognized are approximately 3.2 years and 3.2 years, respectively.

The Company recorded stock-based compensation expense for options issued to non-employees of \$0.2 million and \$0.6 million for the three and nine months ended September 30, 2018, respectively, and \$0.2 million and \$0.5 million for the three and nine months ended September 30, 2017, respectively.

9. Net Loss and Net Loss Per Share

The following table sets forth the computation of the basic and diluted net loss per share (in thousands, except share and per share data):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
Numerator:				
Net loss	\$ (35,371)	\$ (21,844)	\$ (113,773)	\$ (65,298)
Denominator:				
Weighted average common shares outstanding	93,665,231	10,231,036	92,056,812	9,643,686
Net loss per share, basic and diluted	\$ (0.38)	\$ (2.14)	\$ (1.24)	\$ (6.77)

Since the Company was in a loss position for all periods presented, basic net loss per share is the same as diluted net loss per share for all periods as the inclusion of all potential shares of common stock outstanding would have been anti-dilutive. Potentially dilutive securities that were not included in the diluted per share calculations because they would be anti-dilutive were as follows:

	Three and Nine Months Ended September 30,	
	2018	2017
Series A-1 convertible preferred stock	—	46,114,423
Series A-2 convertible preferred stock	—	4,361,527
Series B-1 convertible preferred stock	—	8,124,365
Options issued and outstanding and ESPP shares issuable and outstanding	9,644,444	6,179,687
Restricted shares subject to future vesting	910,452	2,701,059
Early exercised common stock subject to future vesting	182,299	416,669
Shares to be issued under Incro acquisition agreement	—	81,164
Total	10,737,195	67,978,894

10. Subsequent Events

Sanofi

On October 29, 2018, the Company entered into a Collaboration and License Agreement ("Collaboration Agreement") with Genzyme Corporation, a wholly owned subsidiary of Sanofi S.A. ("Sanofi") to develop and commercialize therapeutic products to treat neurological and systemic inflammatory diseases by targeting receptor interacting serine/threonine-protein kinase 1 ("RIPK1"). The two most advanced RIPK1 Inhibitors in the collaboration are DNL747, a potent and selective CNS Product that was discovered by Denali and is currently in Phase 1 testing in healthy volunteers, and DNL758, a Peripheral Product discovered by Denali for which IND-enabling studies have been completed. The Collaboration Agreement will become effective when the requirements of the Hart-Scott-Rodino Antitrust Improvements Act of 1976 have been satisfied.

Under the terms of the Collaboration Agreement, Sanofi will make an upfront cash payment to Denali of \$125.0 million, with future development and commercial milestone payments that could exceed \$1 billion. Sanofi and Denali will share commercial profits and losses from DNL747 in the U.S. and China equally, while Denali will receive a royalty from Sanofi for other territories for DNL747 and worldwide for DNL758. Phase 1b and 2 clinical development costs for DNL747 will be fully funded by Sanofi for Multiple Sclerosis, ALS, and other neurological indications, except for Alzheimer's disease, which will be funded by Denali. Phase 3 trials for all neurological indications will be jointly funded by Sanofi (70%) and Denali (30%). Sanofi will fully fund the clinical development costs for DNL758 in systemic inflammatory diseases.

Lonza

Effective October 2018, the Company executed the second project plan under the Development and Manufacturing Services Agreement with Lonza for approximately \$10.5 million, which covers activities that are expected to take place through December 2024.

Sublease Agreement

On October 18, 2018, the Company entered into a sublease agreement ("Sublease Agreement") to sublease approximately 36,835 rentable square feet of space in its New Premises at 161 Oyster Point in South San Francisco, California. The Sublease Agreement has a term of five years from the commencement date, which is the legal commencement date of the Headquarters Lease Amendment, and provides for the Company to receive monthly base rent amounts escalating over the term of the lease, totaling approximately \$14.8 million over the term of the Sublease Agreement.

ITEM 2. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

The following discussion and analysis of our financial condition and results of operations should be read together with our financial statements and the other financial information appearing elsewhere in this Quarterly Report on Form 10-Q. These statements generally relate to future events or to our future financial performance and involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. The following discussion and analysis contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Our actual results and the timing of events may differ materially from those discussed in our forward-looking statements as a result of various factors, including those discussed below and those discussed in the section entitled "Risk Factors" included in this Quarterly Report on Form 10-Q.

Forward-looking statements include, but are not limited to, statements about:

- the success, cost and timing of our development activities, preclinical studies and clinical trials, including the enrollment in such trials, and in particular the development of our blood-brain barrier ("BBB") platform technology, core programs and biomarkers;*
- the extent to which any dosing limitations that we have been subject to, and/or may be subject to in the future, may affect the success of our product candidates;*
- the impact of preclinical findings on our ability to achieve exposures of our product candidates that allow us to explore a robust pharmacodynamic range of these candidates in humans;*
- the expected potential benefits and potential revenue resulting from strategic collaborations with third parties and our ability to attract collaborators with development, regulatory and commercialization expertise;*
- the timing or likelihood of regulatory filings and approvals;*
- our ability to obtain and maintain regulatory approval of our product candidates, and any related restrictions, limitations and/or warnings in the label of any approved product candidate;*
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates and technology;*
- the terms and conditions of licenses granted to us and our ability to license and/or acquire additional intellectual property relating to our product candidates and BBB platform technology;*
- our ability to obtain funding for our operations, including funding necessary to develop and commercialize our current and potential future product candidates;*
- our plans and ability to establish sales, marketing and distribution infrastructure to commercialize any product candidates for which we obtain approval;*
- future agreements with third parties in connection with the commercialization of our product candidates;*
- the size and growth potential of the markets for our product candidates, if approved for commercial use, and our ability to serve those markets;*
- the rate and degree of market acceptance of our product candidates;*

[Table of Contents](#)

- existing regulations and regulatory developments in the United States and foreign countries;
- potential claims relating to our intellectual property and third-party intellectual property;
- our ability to contract with third-party suppliers and manufacturers and their ability to perform adequately;
- our potential plans and ability to develop our own manufacturing facilities;
- the pricing and reimbursement of our product candidates, if approved and commercialized;
- the success of competing products or platform technologies that are or may become available;
- our ability to attract and retain key managerial, scientific and medical personnel;
- the accuracy of our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- our ability to enhance operational, financial and information management systems;
- our financial performance; and
- our expectations regarding the period during which we qualify as an emerging growth company under the JOBS Act.

These forward-looking statements are subject to a number of risks, uncertainties, and assumptions, including those described in “Risk Factors”. In some cases, you can identify these statements by terms such as “anticipate,” “believe,” “could,” “estimate,” “expects,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “will,” “would” or the negative of those terms, and similar expressions that convey uncertainty of future events or outcomes. These forward-looking statements reflect our beliefs and views with respect to future events and are based on estimates and assumptions as of the date of this Quarterly Report on Form 10-Q and are subject to risks and uncertainties. We discuss many of these risks in greater detail in the section entitled “Risk Factors” included in Part II, Item 1A and elsewhere in this report. Moreover, we operate in a very competitive and rapidly changing environment. New risks emerge from time to time. It is not possible to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. Given these uncertainties, you should not place undue reliance on these forward-looking statements. We qualify all of the forward-looking statements in this Quarterly Report on Form 10-Q by these cautionary statements. Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to update the reasons actual results could differ materially from those anticipated in any forward-looking statements, whether as a result of new information, future events or otherwise.

Overview

Our goal is to discover and develop therapeutics to defeat degeneration.

Our strategy is guided by three overarching principles:

- **Genetic Pathway Potential:** We select our therapeutic targets and disease pathways based on genes that, when mutated, cause, or are major risk factors for, neurodegenerative diseases, which we refer to as degenogenes.
- **Engineering Brain Delivery:** We engineer our product candidates to cross the BBB and act directly in the brain.
- **Biomarker-Driven Development:** We discover, develop and utilize biomarkers to select the right patient population and demonstrate target engagement, pathway engagement and impact on disease progression of our product candidates.

Our portfolio currently consists of thirteen programs. To prioritize the allocation of our resources, we designate certain programs as core programs and others as seed programs, and we currently have eight core programs and five seed programs. Our most advanced core programs are our leucine-rich repeat kinase 2 ("LRRK2") inhibitor program to address Parkinson's disease and our receptor interacting serine/threonine protein kinase 1 ("RIPK1") inhibitor program to address Alzheimer's disease and amyotrophic lateral sclerosis ("ALS"). The two most advanced product candidates in our LRRK2 program, DNL201 and DNL151, are potent, selective and brain-penetrant small molecule LRRK2 inhibitor product candidates for Parkinson's disease. We have announced that DNL201 meets all key objectives in its Phase 1 Healthy Volunteer Study, including achieving targeted levels of cerebrospinal fluid (CSF) exposure, robust target engagement as measured by two blood-based biomarkers of LRRK2 activity at doses that were safe and well tolerated, and effects on biomarkers of lysosomal function. On October 25, 2018 data was presented at the Michael J. Fox Foundation Parkinson's Disease Therapeutic Conference, and recruitment has commenced for the DNL201 Phase 1b clinical study in Parkinson's disease patients with and without the genetic LRRK2 mutation, with the first patient expected to be dosed in late 2018. DNL151 is currently in a Phase 1 clinical trial in healthy volunteers in the Netherlands. The most advanced product candidate in our RIPK1 inhibitor program, DNL747, is a potent, selective and brain-penetrant small molecule RIPK1 inhibitor product candidate for ALS and Alzheimer's disease is currently in a Phase 1 clinical trial in healthy volunteers in the Netherlands.

We have also developed proprietary BBB platform technology, our transport vehicle ("TV"), which is designed to effectively transport antibodies (antibody transport vehicle ("ATV")) and enzymes (enzyme transport vehicle ("ETV")) across the BBB. This technology is designed to engage specific BBB transport receptors, which are ubiquitously expressed in brain capillaries and facilitate transport of proteins into the brain. We are currently optimizing and broadening this platform technology. We plan to have multiple product candidates that utilize our ATV or ETV platforms enter clinical development in 2019 and 2020, including molecules targeting alpha-synuclein ("aSyn"); iduronate 2-sulfatase ("IDS"); triggering receptor expressed in myeloid cells 2 ("TREM2"); and a bispecific agent targeting both beta-secretase 1 ("BACE1"); and Tau.

To complement our internal capabilities, we have entered into arrangements with biopharmaceutical companies, numerous leading academic institutions and foundations to gain access to new product candidates, enable and accelerate the development of our existing programs and deepen our scientific understanding of certain areas of biology. We rely on third-party contract manufacturers to manufacture and supply our preclinical and clinical materials to be used during the development of our product candidates. We currently do not need commercial manufacturing capacity.

Since we commenced operations in May 2015, we have devoted substantially all of our resources to discovering, acquiring and developing product candidates, building our BBB platform technology and assembling our core capabilities in neurodegenerative disease pathways.

[Table of Contents](#)

Key operational and financing milestones in 2018 to date include:

- On January 3, 2018, we entered into the Takeda Collaboration Agreement pursuant to which we granted Takeda an option with respect to three of our programs to develop and commercialize, jointly with us, certain biologic products that are enabled by our BBB delivery technology and intended for the treatment of neurodegenerative disorders. Pursuant to this agreement, we received an upfront payment of \$40.0 million in February 2018, as well as the first preclinical milestone payment of \$5.0 million related to one of our programs. Further, under the associated common stock purchase agreement (the "Stock Purchase Agreement"), we received proceeds of \$110.0 million for the sale of 4,214,559 shares of our common stock which were issued on February 23, 2018.
- On February 7, 2018, we submitted a CTA for DNL747, a RIPK1 inhibitor, to the Netherlands Health Authority, and we initiated a Phase 1 clinical trial of DNL747 in healthy volunteers in the Netherlands in March 2018.
- On May 21, 2018, we exercised our right to nominate two additional Fcab (constant Fc-domains with antigen-binding activity) targets under the F-star Collaboration Agreement associated with our BBB platform technology, resulting in an obligation to make a one-time payment of \$6.0 million within 90 days of the exercise date.
- On May 30, 2018, we exercised our buy-out option to acquire all of the outstanding shares of F-star Gamma Limited, and subsequently changed the name of the entity to Denali BBB Holding Limited. We made initial exercise payments of, in the aggregate, \$18.0 million, less the estimated net liabilities of F-star Gamma, which was approximately \$0.2 million. In addition, we are required under the buy-out option agreement and the F-star Gamma License to make future contingent payments to F-star Ltd or the former shareholders of F-star Gamma, up to a maximum amount of \$447.0 million in the aggregate, upon the achievement of certain defined preclinical, clinical, regulatory and commercial milestones.
- During the second quarter of 2018, one of our pending patent applications directed to the composition of matter of DNL151, a LRRK2 inhibitor, issued in the United States.
- During the second quarter of 2018 we achieved *in vivo* proof of concept for the ETV:IDS program in a mouse model of Hunter Syndrome.
- On August 1, 2018, we announced positive results from the DNL201 Phase 1 Healthy Volunteer Study and data from this study was presented at the Michael J Fox Foundation Parkinson's Disease Therapeutic Conference on October 25, 2018. Recruitment has commenced for the Phase 1b clinical study in Parkinson's disease patients with and without the genetic LRRK2 mutation, with the first patient expected to be dosed in late 2018.
- On October 7, 2018, we confirmed the first preclinical milestone was met for the third identified discovery stage program under the Takeda Collaboration Agreement, triggering a milestone payment of \$5.0 million, which we expect to receive in November 2018.
- On October 29, 2018, we entered into a Collaboration and License Agreement with Genzyme Corporation, a wholly owned subsidiary of Sanofi S.A. ("Sanofi") to develop and commercialize therapeutic products to treat neurological and systemic inflammatory diseases by targeting receptor interacting serine/threonine-protein kinase 1 ("RIPK1"). Denali will receive an upfront fee of \$125 million and contingent milestone payments that could exceed \$1 billion. For products intended to treat neurological diseases, Denali and Sanofi will share development costs and commercial profits and losses in the United States and China, while Denali will receive a royalty from Sanofi for other territories. For products intended to treat systemic inflammatory diseases, Sanofi will pay all development costs and Denali will receive a royalty worldwide. The Sanofi Collaboration Agreement will become effective when the requirements of the Hart-Scott-Rodino Antitrust Improvements Act of 1976 have been satisfied.

[Table of Contents](#)

We do not have any products approved for sale and have not generated any product revenue since our inception. We have funded our operations primarily from the issuance and sale of convertible preferred stock, the proceeds from our IPO and cash proceeds from Takeda under the Takeda Collaboration Agreement.

We have incurred significant operating losses to date and expect to continue to incur operating losses for the foreseeable future. Our net losses were \$35.4 million and \$113.8 million for the three and nine months ended September 30, 2018, and \$21.8 million and \$65.3 million for the three and nine months ended September 30, 2017, respectively. As of September 30, 2018, we had an accumulated deficit of \$305.5 million. We expect to continue to incur significant expenses and operating losses as we advance our LRRK2 and RIPK1 programs through clinical trials; broaden and improve our BBB platform technology; acquire, discover, validate and develop additional product candidates; obtain, maintain, protect and enforce our intellectual property portfolio; and hire additional personnel.

Components of Operating Results

Collaboration Revenue

To date, we have not generated any revenue from product sales and do not expect to generate any revenue from product sales for the foreseeable future. For the three and nine months ended September 30, 2018, we recognized \$1.2 million and \$3.5 million, respectively, of collaboration revenue from the Takeda Collaboration Agreement.

In the future, we will continue to recognize revenue from the Takeda Collaboration Agreement and may generate revenue from product sales or other collaboration agreements, strategic alliances and licensing arrangements, including the Sanofi Collaboration Agreement. We expect that our revenue will fluctuate from quarter-to-quarter and year-to-year as a result of the timing and amount of license fees, milestones, reimbursement of costs incurred and other payments and product sales, to the extent any are successfully commercialized. If we fail to complete the development of our product candidates in a timely manner or obtain regulatory approval for them, our ability to generate future revenue, and our results of operations and financial position, would be materially adversely affected.

Operating Expenses

Research and Development

Research and development activities account for a significant portion of our operating expenses. We record research and development expenses as incurred. Research and development expenses incurred by us for the discovery and development of our product candidates and BBB platform technology include:

- external research and development expenses, including:
- expenses incurred under arrangements with third parties, such as contract research organizations ("CROs"), preclinical testing organizations, contract manufacturing organizations ("CMOs"), academic and non-profit institutions and consultants;
- expenses to acquire technologies to be used in research and development that have not reached technological feasibility and have no alternative future use;
- fees related to our license and collaboration agreements;
- personnel-related expenses, including salaries, benefits and non-cash stock-based compensation expense; and

[Table of Contents](#)

- other expenses, which include direct and allocated expenses for laboratory, facilities and other costs.

A portion of our research and development expenses are direct external expenses, which we track on a program-specific basis once a program has commenced a late-stage IND-enabling studies.

Program expenses include expenses associated with our most advanced product candidates and the discovery and development of backup or next-generation molecules. We also track external expenses associated with our BBB platform technology. All external costs associated with earlier stage programs, or that benefit the entire portfolio, are tracked as a group. We do not track personnel or other operating expenses incurred for our research and development programs on a program-specific basis. These expenses primarily relate to salaries and benefits, stock-based compensation, facility expenses including depreciation and lab consumables.

At this time, we cannot reasonably estimate or know the nature, timing and estimated costs of the efforts that will be necessary to complete the development of, and obtain regulatory approval for, any of our product candidates. We are also unable to predict when, if ever, material net cash inflows will commence from sales or licensing of our product candidates. This is due to the numerous risks and uncertainties associated with drug development, including the uncertainty of:

- our ability to add and retain key research and development personnel;
- our ability to establish an appropriate safety profile with IND-enabling toxicology studies;
- our ability to successfully develop, obtain regulatory approval for, and then successfully commercialize, our product candidates;
- our successful enrollment in and completion of clinical trials;
- the costs associated with the development of any additional product candidates we identify in-house or acquire through collaborations;
- our ability to discover, develop and utilize biomarkers to demonstrate target engagement, pathway engagement and the impact on disease progression of our molecules;
- our ability to establish agreements with third-party manufacturers for clinical supply for our clinical trials and commercial manufacturing, if our product candidates are approved;
- the terms and timing of any collaboration, license or other arrangement, including the terms and timing of any milestone payments thereunder;
- our ability to obtain and maintain patent, trade secret and other intellectual property protection and regulatory exclusivity for our product candidates if and when approved;
- our receipt of marketing approvals from applicable regulatory authorities;
- our ability to commercialize products, if and when approved, whether alone or in collaboration with others; and
- the continued acceptable safety profiles of the product candidates following approval.

[Table of Contents](#)

A change in any of these variables with respect to the development of any of our product candidates would significantly change the costs, timing and viability associated with the development of that product candidate. We expect our research and development expenses to increase at least over the next several years as we continue to implement our business strategy, advance our current programs, expand our research and development efforts, seek regulatory approvals for any product candidates that successfully complete clinical trials, access and develop additional product candidates and incur expenses associated with hiring additional personnel to support our research and development efforts. In addition, product candidates in later stages of clinical development generally incur higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials.

General and Administrative

General and administrative expenses include personnel-related expenses, such as salaries, benefits, travel and non-cash stock-based compensation expense, expenses for outside professional services and allocated expenses. Outside professional services consist of legal, accounting and audit services and other consulting fees. Allocated expenses consist of rent expenses related to our office and research and development facility not otherwise included in research and development expenses. We expect to incur additional expenses as a result of operating as a public company, including expenses related to compliance with the rules and regulations of the SEC and those of any national securities exchange on which our securities are traded, additional insurance expenses, investor relations activities and other administrative and professional services. We also expect to increase our administrative headcount as we advance our product candidates through clinical development, which will also likely require us to increase our general and administrative expenses.

Interest and Other Income, Net

Interest and other income, net, consists primarily of interest income and investment income earned on our cash, cash equivalents, and marketable securities as well as unrealized gains and losses on foreign currency hedges.

Results of Operations

Comparison of the three and nine months ended September 30, 2018 and 2017

The following tables set forth the significant components of our results of operations (in thousands):

	Three Months Ended September 30,		Change	
	2018	2017	\$	%
Collaboration revenue	\$ 1,195	\$ —	\$ 1,195	* %
Operating expenses:				
Research and development	30,321	18,515	11,806	64
General and administrative	8,838	3,773	5,065	134
Total operating expenses	39,159	22,288	16,871	76
Loss from operations	(37,964)	(22,288)	(15,676)	70
Interest and other income, net	2,593	444	2,149	484
Net loss	\$ (35,371)	\$ (21,844)	\$ (13,527)	62 %

* Percentage is not meaningful.

[Table of Contents](#)

	Nine Months Ended September 30,		Change	
	2018	2017	\$	%
Collaboration revenue	\$ 3,484	\$ —	\$ 3,484	* %
Operating expenses:				
Research and development	103,274	55,989	47,285	84
General and administrative	21,304	10,611	10,693	101
Total operating expenses	124,578	66,600	57,978	87
Loss from operations	(121,094)	(66,600)	(54,494)	82
Interest and other income, net	7,321	1,302	6,019	462
Net loss	\$ (113,773)	\$ (65,298)	\$ (48,475)	74 %

* Percentage is not meaningful.

Collaboration Revenue. Collaboration Revenue was \$1.2 million and \$3.5 million for the three and nine months ended September 30, 2018, respectively, with no revenue recognized for the three and nine months ended September 30, 2017. The increase was due to revenue recognized under our Takeda Collaboration Agreement.

Research and development expenses. Research and development expenses were \$30.3 million and \$103.3 million for the three and nine months ended September 30, 2018, respectively, compared to \$18.5 million and \$56.0 million for the three and nine months ended September 30, 2017, respectively.

The following table summarizes our research and development expenses by program and category (in thousands):

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2018	2017	2018	2017
LRRK2 program external expenses ⁽¹⁾	\$ 3,912	\$ 2,054	\$ 10,159	\$ 11,803
RIPK1 program external expenses	2,745	3,624	7,692	7,379
BBB platform external expenses ⁽²⁾	956	1,021	29,153	2,655
Other external research and development expenses	5,727	2,759	13,973	7,663
Personnel-related expenses ⁽³⁾	11,122	5,816	28,220	16,713
Other unallocated research and development expenses	5,859	3,241	14,077	9,776
Total research and development expenses	\$ 30,321	\$ 18,515	\$ 103,274	\$ 55,989

(1) The amount for the nine months ended September 30, 2017 includes a milestone payment of \$2.5 million under the license agreement with Genentech.

(2) The amount for the nine months ended September 30, 2018 includes the upfront purchase price less estimated net liabilities acquired of \$17.8 million, and transaction costs of \$1.9 million in relation to our acquisition of F-star Gamma Limited, and the \$6.0 million one-time payment made to F-star Ltd to nominate two additional Fcab targets under the Collaboration Agreement.

(3) Personnel-related expenses include stock-based compensation expense of \$2.9 million and \$7.2 million for the three and nine months ended September 30, 2018, respectively, and \$0.7 million and \$1.9 million for the three and nine months ended September 30, 2017, respectively, reflecting an increase of \$2.2 million and \$5.2 million, respectively.

[Table of Contents](#)

The increase in total research and development expenses of \$11.8 million for the three months ended September 30, 2018 compared to the three months ended September 30, 2017 was primarily attributable to a \$5.3 million increase in personnel-related expenses, consisting of a \$3.1 million increase in salaries and related expenses attributable to an increase in our research and development headcount, and a \$2.2 million increase in stock-based compensation expense attributable to new options granted at higher exercise prices subsequent to the IPO and an increase in our research and development headcount. Further, there was a \$3.0 million increase in other external research and development expenses, which reflects our increased investment in growing and developing our pipeline, and an increase in other unallocated research and development expenses of \$2.6 million, which was primarily due to an increase in facilities related expenses of \$1.9 million primarily due to rent expense associated with the new headquarters lease, and an increase in lab consumable expenses of \$0.6 million attributable to increases in research and development headcount. There was also an increase of \$1.9 million in LRRK2 program expenses due to increased costs associated with Phase 1 clinical trials in healthy volunteers.

These increases were partially offset by a \$0.9 million decrease in RIPK1 program external expenses due to significant expenses incurred in the three months ended September 30, 2017 to manufacture DNL747 for the Phase 1 clinical trial in healthy volunteers which commenced in early 2018.

The increase in total research and development expenses of \$47.3 million for the nine months ended September 30, 2018 compared to the nine months ended September 30, 2017 was primarily attributable to a \$26.5 million increase in BBB platform external expenses, the majority of which related to expense associated with the acquisition of F-star Gamma Limited as well as the nomination of two additional Fcab targets under the F-star Collaboration Agreement. Personnel-related expenses increased by \$11.5 million, consisting of a \$6.3 million increase in salaries and related expenses attributable to an increase in our research and development headcount, and a \$5.2 million increase in stock-based compensation expense attributable to new options granted at higher valuations subsequent to the IPO, and an increase in our research and development headcount. Further, there was a \$6.3 million increase in other external research and development expenses, which reflects our increased investment in growing and developing our pipeline, and an increase in other unallocated research and development expenses of \$4.3 million, which was primarily due to an increase in facilities related expenses of \$2.6 million primarily due to rent expense associated with the new headquarters lease and an increase in lab consumable expenses of \$1.5 million attributable to increases in research and development headcount. These increases were partially offset by a \$1.6 million decrease in LRRK2 program external expenses, primarily due to the milestone payment of \$2.5 million under the license agreement with Genentech included in the nine months ended September 30, 2017.

General and administrative expenses. General and administrative expenses were \$8.8 million for the three months ended September 30, 2018 compared to \$3.8 million for the three months ended September 30, 2017, including stock-based compensation expense of \$2.6 million and \$0.4 million in the three months ended September 30, 2018 and 2017, respectively. The increase of approximately \$5.0 million was primarily attributable to the \$2.2 million increase in stock-based compensation expense mainly due to new options granted at exercise prices subsequent to the IPO and an increase in our general and administrative headcount, a \$1.0 million increase in other personnel-related expenses due to an increase in our general and administrative headcount, and a \$0.9 million increase in legal expenses and other professional services to support our ongoing operations as a public company.

General and administrative expenses were \$21.3 million for the nine months ended September 30, 2018 compared to \$10.6 million for the nine months ended September 30, 2017, including stock-based compensation expense of \$6.0 million and \$1.0 million in the nine months ended September 30, 2018 and 2017, respectively. The increase of \$10.7 million was primarily attributable to the \$5.0 million increase in stock-based compensation expense mainly due to new options granted at higher exercise prices subsequent to the IPO and an increase in our general and administrative headcount, a \$2.1 million increase in other personnel-related expenses due to an increase in our general and administrative headcount, and a \$1.8 million increase in legal expenses and other professional services to support our ongoing operations as a public company.

[Table of Contents](#)

Interest and other income, net. Interest and other income, net was \$2.6 million for the three months ended September 30, 2018 compared to \$0.4 million for the three months ended September 30, 2017. The increase of \$2.2 million reflects that the marketable securities balances were higher in 2018 than in 2017, and increased interest rates on marketable securities in our portfolio for the three months ended September 30, 2018.

Interest and other income, net was \$7.3 million for the nine months ended September 30, 2018 compared to \$1.3 million for the nine months ended September 30, 2017. The increase of \$6.0 million reflects that the marketable securities balances were higher in 2018 than in 2017, and that there were increased interest rates on marketable securities in our portfolio for the nine months ended September 30, 2018.

Liquidity and Capital Resources

Sources of Liquidity

We have funded our operations primarily from the issuance and sale of convertible preferred stock, the proceeds from our IPO and cash proceeds under our Takeda Collaboration Agreement. In December 2017, we completed our IPO pursuant to which we issued 15,972,221 shares of our common stock, including 2,083,333 shares sold pursuant the underwriters' full exercise of their option to purchase additional shares, at a price of \$18.00 per share. We received \$264.3 million from our IPO, net of underwriting discounts and commissions, and offering expenses incurred by us.

Pursuant to the Takeda Collaboration Agreement, we received a \$40.0 million upfront payment and a \$5.0 million preclinical milestone in February 2018. Further, under the associated Stock Purchase Agreement we received a further \$110.0 million of cash proceeds in February 2018 in exchange for 4,214,559 shares of common stock issued.

As of September 30, 2018, we had cash, cash equivalents and marketable securities in the amount of \$517.1 million.

Future Funding Requirements

To date, we have not generated any product revenue. We do not expect to generate any product revenue unless and until we obtain regulatory approval of and commercialize any of our product candidates, and we do not know when, or if, either will occur.

We expect to continue to incur substantial additional losses for the foreseeable future as we expand our research and development activities and continue the development of, and seek regulatory approvals for, our product candidates, and begin to commercialize any approved products. Further, we expect general and administrative expenses to increase as we will now incur additional costs associated with operating as a public company. We are subject to all of the risks typically related to the development of new product candidates, and we may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that may adversely affect our business. We anticipate that we will need substantial additional funding in connection with our continuing operations.

[Table of Contents](#)

Until we can generate a sufficient amount of revenue from the commercialization of our product candidates or from our Takeda Collaboration Agreement, Sanofi Collaboration Agreement, or future agreements with other third parties, if ever, we expect to finance our future cash needs through public or private equity or debt financings. Additional capital may not be available on reasonable terms, if at all. If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of one or more of our product candidates. If we raise additional funds through the issuance of additional debt or equity securities, it could result in dilution to our existing stockholders, increased fixed payment obligations and the existence of securities with rights that may be senior to those of our common stock. If we incur indebtedness, we could become subject to covenants that would restrict our operations and potentially impair our competitiveness, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. Additionally, any future collaborations we enter into with third parties may provide capital in the near term but limit our potential cash flow and revenue in the future. Any of the foregoing could significantly harm our business, financial condition and prospects.

Since our inception, we have incurred significant losses and negative cash flows from operations. We have an accumulated deficit of \$305.5 million through September 30, 2018. We expect to incur substantial additional losses in the future as we conduct and expand our research and development activities. We believe that our existing cash, cash equivalents and marketable securities will be sufficient to enable us to fund our projected operations through at least the next 12 months. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect. Our future funding requirements will depend on many factors, including:

- the timing and progress of preclinical and clinical development activities;
- the number and scope of preclinical and clinical programs we decide to pursue;
- the progress of the development efforts of third parties with whom we have entered into license and collaboration agreements;
- our ability to maintain our current research and development programs and to establish new research and development, license or collaboration arrangements;
- our ability and success in securing manufacturing relationships with third parties or, in the future, in establishing and operating a manufacturing facility;
- the costs involved in prosecuting, defending and enforcing patent claims and other intellectual property claims;
- the cost and timing of regulatory approvals;
- our efforts to enhance operational, financial and information management systems and hire additional personnel, including personnel to support development of our product candidates; and
- the costs and ongoing investments to in-license and/or acquire additional technologies.

A change in the outcome of any of these or other variables with respect to the development of any of our product candidates could significantly change the costs and timing associated with the development of that product candidate. Furthermore, our operating plans may change in the future, and we may need additional funds to meet operational needs and capital requirements associated with such operating plans.

Cash Flows

The following table sets forth a summary of the primary sources and uses of cash for each of the periods presented below (in thousands):

	Nine Months Ended September 30,	
	2018	2017
Net cash used in operating activities	\$ (43,069)	\$ (58,299)
Net cash (used in) provided by investing activities	(226,019)	53,983
Net cash provided by financing activities	95,329	732
Net decrease in cash, cash equivalents and restricted cash	\$ (173,759)	\$ (3,584)

Net Cash Used In Operating Activities

During the nine months ended September 30, 2018, cash used in operating activities was \$43.1 million, which consisted of a net loss of \$113.8 million, adjusted by non-cash expenses of \$16.3 million and cash provided by changes in our operating assets and liabilities of \$54.4 million. The non-cash expenses consisted primarily of stock-based compensation expense of \$13.1 million and depreciation expense of \$5.0 million partially offset by net amortization of premiums and discounts on marketable securities of \$1.9 million. The change in our operating assets and liabilities was primarily due to an increase of \$57.1 million in the contract liability related to the Takeda Collaboration Agreement, an increase of \$2.6 million in accrued and other current liabilities, and an increase in accounts payable of \$1.2 million, partially offset by an increase of \$5.4 million in prepaid expenses and other assets, and a decrease of \$1.2 million in deferred rent.

During the nine months ended September 30, 2017, cash used in operating activities was \$58.3 million, which consisted of a net loss of \$65.3 million, adjusted by non-cash expenses of \$6.1 million and cash provided by changes in our operating assets and liabilities of \$0.9 million. The non-cash charges consisted primarily of stock-based compensation expense of \$3.0 million and depreciation expense of \$2.3 million. The change in our operating assets and liabilities was primarily due to an increase of \$0.9 million in accrued and other current liabilities.

Net Cash (Used In) Provided By Investing Activities

During the nine months ended September 30, 2018, cash used in investing activities was \$226.0 million, which consisted of \$400.6 million of purchases of marketable securities and \$2.0 million of capital expenditures to purchase property and equipment, partially offset by \$176.6 million in proceeds from the maturity of marketable securities.

During the nine months ended September 30, 2017, cash provided by investing activities was \$54.0 million, which consisted of \$102.4 million in proceeds from the maturity of marketable securities, partially offset by \$46.7 million of purchases of marketable securities and \$1.8 million of capital expenditures to purchase property and equipment.

Net Cash Provided By Financing Activities

During the nine months ended September 30, 2018, cash provided by financing activities was \$95.3 million, which consisted of the \$94.4 million market value of the 4,214,559 shares of common stock issued to Takeda in February 2018 under the Stock Purchase Agreement, and \$2.3 million of proceeds from the exercise of options to purchase common stock and issuance of ESPP shares. These amounts were partially offset by \$1.4 million for payments of issuance costs related to the issuance of common and preferred stock.

During the nine months ended September 30, 2017, cash provided by financing activities was \$0.7 million, which consisted of net proceeds in connection with exercises of options to purchase common stock.

Off-Balance Sheet Arrangements

We have not entered into any off-balance sheet arrangements. Prior to our acquisition of all of the outstanding shares of F-star Gamma, our F-star Collaboration Agreement represented a variable interest in a variable interest entity, or VIE, F-star Gamma. However, we did not consolidate F-star Gamma in our consolidated financial statements because we had determined that we were not considered to be its primary beneficiary.

Contractual Obligations and Commitments

Effective September 2017, we entered into a Development and Manufacturing Services Agreement, as amended (the "DMSA"), with Lonza Sales AG ("Lonza") for the development and manufacture of biologic products. Under the DMSA, we will execute purchase orders based on project plans authorizing Lonza to provide development and manufacturing services with respect to certain of our antibody and enzyme products, and will pay for the services provided and batches delivered in accordance with the DMSA and project plan. Unless earlier terminated, the Lonza agreement will expire on September 6, 2022. As of September 30, 2018, we had several purchase orders for biological product development and manufacturing costs totaling \$13.0 million. The activities under these purchase orders are expected to be completed by April 2024. During the three and nine months ended September 30, 2018, we incurred costs of \$1.4 million and \$2.6 million, respectively, and made payments of \$1.3 million and \$2.0 million, respectively, for the development and manufacturing services rendered under the agreement. As of September 30, 2018, we had total non-refundable purchase commitments of \$7.7 million under the DMSA.

Effective October 2018, we initiated the second project plan under the DMSA, which included services totaling \$10.5 million for the development and manufacture of biologic products, the activities under which commenced in October 2018 and are expected to be completed by December 2024. As of November 2, 2018 we had total non-refundable purchase commitments of \$5.5 million related to the second project plan.

On May 2, 2018, we entered into an amendment to our Headquarters Lease (the "Headquarters Lease Amendment") to relocate and expand our headquarters to 148,020 rentable square feet in a to-be-constructed building in South San Francisco, California (the "New Premises"). The Headquarters Lease Amendment has a contractual term of ten years from the legal commencement date, which is the later of February 1, 2019 or the date that the premises are ready for occupancy. We have an option to extend the lease term for a period of ten years by giving the landlord written notice of the election to exercise the option at least nine months, but not more than twelve months, prior to the expiration of the Headquarters Lease Amendment lease term.

Under the terms of the Headquarters Lease Amendment, we were required to increase the security deposit of \$0.5 million to \$1.5 million. The Headquarters Lease Amendment provides for monthly base rent amounts escalating over the term of the lease. In addition, the Headquarters Lease Amendment provides a tenant improvement allowance ("TIA") of up to \$25.9 million, of which \$4.4 million, if utilized, would be repaid to the landlord in the form of additional monthly rent with interest applied. We will also be required to pay our share of operating expenses for the New Premises.

Other than those detailed above, there have been no other material changes from the contractual obligations and commitments previously disclosed in our Annual Report on Form 10-K for the year ended December 31, 2017, as filed with the SEC on March 19, 2018.

Critical Accounting Policies and Significant Judgments and Estimates

This discussion and analysis of our financial condition and results of operations is based on our condensed consolidated financial statements, which have been prepared in accordance with generally accepted accounting principles in the United States. The preparation of these condensed consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the condensed consolidated financial statements, as well as the reported revenues recognized and expenses incurred during the reporting periods. Our estimates are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

Other than the addition of the revenue recognition policy included below, there have been no material changes to our critical accounting policies and estimates during the nine months ended September 30, 2018 from those described in "Management's Discussion and Analysis of Financial Condition and Results of Operations" included in our 2017 Annual Report on Form 10-K for the year ended December 31, 2017, as filed with the SEC on March 19, 2018.

Revenue Recognition

License and Collaboration Revenues

We analyze our collaboration arrangements to assess whether they are within the scope of ASC 808, Collaborative Arrangements ("ASC 808") to determine whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities. This assessment is performed throughout the life of the arrangement based on changes in the responsibilities of all parties in the arrangement. For collaboration arrangements within the scope of ASC 808 that contain multiple elements, we first determine which elements of the collaboration are deemed to be within the scope of ASC 808 and those that are more reflective of a vendor-customer relationship and, therefore, within the scope of Topic 606. For elements of collaboration arrangements that are accounted for pursuant to ASC 808, an appropriate recognition method is determined and applied consistently, generally by analogy to Topic 606. The accounting treatment pursuant to Topic 606 is outlined below.

The terms of licensing and collaboration agreements entered into typically include payment of one or more of the following: non-refundable, up-front license fees; development, regulatory and commercial milestone payments; payments for manufacturing supply services; and royalties on net sales of licensed products. Each of these payments results in license, collaboration and other revenues, except for revenues from royalties on net sales of licensed products, which are classified as royalty revenues. The core principle of Topic 606 is to recognize revenues when promised goods or services are transferred to customers in an amount that reflects the consideration that is expected to be received in exchange for those goods or services.

In determining the appropriate amount of revenue to be recognized as we fulfill our obligations under each of our agreements, we perform the following steps: (i) identify the promised goods or services in the contract; (ii) determine whether the promised goods or services are performance obligations including whether they are distinct in the context of the contract; (iii) measure the transaction price, including the constraint on variable consideration; (iv) allocate the transaction price to the performance obligations based on estimated selling prices; and (v) recognize revenue when (or as) we satisfy each performance obligation.

[Table of Contents](#)

We record amounts received prior to satisfying the revenue recognition criteria as contract liabilities in our consolidated balance sheets. If the related performance obligation is expected to be satisfied within the next twelve months this will be classified in current liabilities. Amounts recognized as revenue prior to receipt are recorded as contract assets in our consolidated balance sheets. If we expect to have an unconditional right to receive the consideration in the next twelve months this will be classified in current assets. We present a net contract asset or liability for each contract with a customer.

At contract inception, we assess the goods or services promised in a contract with a customer and identify those distinct goods and services that represent a performance obligation. A promised good or service may not be identified as a performance obligation if it is immaterial in the context of the contract with the customer, if it is not separately identifiable from other promises in the contract (either because it is not capable of being separated or because it is not separable in the context of the contract), or if the performance obligation does not provide the customer with a material right.

We consider the terms of the contract and our customary business practices to determine the transaction price. The transaction price is the amount of consideration to which we expect to be entitled in exchange for transferring promised goods or services to a customer. The consideration promised in a contract with a customer may include fixed amounts, variable amounts, or both. Variable consideration will only be included in the transaction price when it is not considered constrained, which is when it is probable that a significant reversal in the amount of cumulative revenue recognized will not occur.

If it is determined that multiple performance obligations exist, at the inception of the agreement we will allocate the transaction price to all identified performance obligations based on the relative standalone selling prices. We estimate the relative selling price for each deliverable using objective evidence if it is available. If objective evidence is not available, we use our best estimate of the selling price for the deliverable.

Revenue is recognized when, or as, we satisfy a performance obligation by transferring a promised good or service to a customer. An asset is transferred when, or as, the customer obtains control of that asset, which for a service is considered to be as the services are received and used. We recognize revenue over time by measuring the progress toward complete satisfaction of the relevant performance obligation using an appropriate input or output method based on the nature of the good or service promised to the customer.

After contract inception, we reassess the transaction price at every period end, and update for changes such as resolution of uncertain events. Any change in the transaction price is allocated to the performance obligations on the same basis as at contract inception.

We may be required to exercise considerable judgment in estimating revenue to be recognized. Judgment is required in identifying performance obligations, estimating the transaction price, estimating the stand-alone selling prices of identified performance obligations, which may include forecasted revenues, development timelines, reimbursement rates for personnel costs, discount rates and probabilities of technical and regulatory success, and estimating the progress towards satisfaction of performance obligations.

Recent Accounting Pronouncements

Except as described in Note 1 to the condensed consolidated financial statements under the headings "Recently Issued Accounting Pronouncements" and "Recently Adopted Accounting Pronouncements", there have been no new accounting pronouncements or changes to accounting pronouncements during the nine months ended September 30, 2018, as compared to the recent accounting pronouncements described in our 2017 Annual Report on Form 10-K for the year ended December 31, 2017, as filed with the SEC on March 19, 2018, that are of significance or potential significance to us.

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

We are exposed to market risks in the ordinary course of our business, primarily related to interest rate and foreign currency sensitivities.

Interest Rate Sensitivity

We are exposed to market risk related to changes in interest rates. We had cash, cash equivalents and marketable securities of \$517.1 million as of September 30, 2018, which consisted primarily of money market funds and marketable securities, largely composed of investment grade, short to intermediate term fixed income securities.

The primary objective of our investment activities is to preserve capital to fund our operations. We also seek to maximize income from our investments without assuming significant risk. To achieve our objectives, we maintain a portfolio of investments in a variety of securities of high credit quality and short-term duration, according to our board-approved investment charter. Our investments are subject to interest rate risk and could fall in value if market interest rates increase. A hypothetical 10% relative change in interest rates during any of the periods presented would not have had a material impact on our condensed consolidated financial statements.

Foreign Currency Sensitivity

The majority of our transactions occur in U.S. dollars. However, we do have certain transactions that are denominated in currencies other than the U.S. dollar, primarily British Pounds, Swiss Francs and the Euro, and we therefore are subject to foreign exchange risk. The fluctuation in the value of the U.S. dollar against other currencies affects the reported amounts of expenses, assets and liabilities associated with a limited number of preclinical and clinical activities.

To partially mitigate the impact of changes in currency exchange rates on cash flows from our foreign currency denominated operating expenses, we enter into forward foreign currency exchange contracts. Generally, the market risks of these contracts are offset by the corresponding gains and losses on the transactions being hedged.

We do not use derivative financial instruments for speculative trading purposes, nor do we hedge foreign currency exchange rate exposure in a manner that entirely offsets the effects of changes in foreign currency exchange rates. The counterparties to these forward foreign currency exchange contracts are creditworthy multinational commercial banks, which minimizes the risk of counterparty nonperformance. We regularly review our hedging program and may, as part of this review, make changes to the program.

As of September 30, 2018, we had open forward foreign currency exchange contracts with notional amounts of \$7.3 million. A hypothetical 10% strengthening in foreign currency exchange rates compared with the U.S. dollar relative to exchange rates at September 30, 2018 would have resulted in a reduction in the value received over the remaining life of these contracts of approximately \$0.7 million and, if realized, would negatively affect earnings during the remaining life of the contracts. This analysis does not consider the impact of the hypothetical changes in foreign currency rates would have on the forecasted transactions that these foreign currency sensitive instruments were designated to offset.

ITEM 4. CONTROLS AND PROCEDURES

Evaluation of Disclosure Controls and Procedures

As of September 30, 2018, management, with the participation of our Chief Executive Officer and Chief Financial Officer, performed an evaluation of the effectiveness of the design and operation of our disclosure controls and procedures as defined in Rules 13a-15(e) and 15d-15(e) of the Exchange Act. Our disclosure controls and procedures are designed to ensure that information required to be disclosed in the reports we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including the Chief Executive Officer and the Chief Financial Officer, to allow timely decisions regarding required disclosures.

Any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objective and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that, as of September 30, 2018, the design and operation of our disclosure controls and procedures were effective at a reasonable assurance level.

Changes in Internal Control over Financial Reporting

There was no change in our internal control over financial reporting identified in connection with the evaluation required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the quarter ended September 30, 2018 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

PART II. OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

From time to time, we may become involved in litigation or other legal proceedings. We are not currently a party to any litigation or legal proceedings that, in the opinion of our management, are likely to have a material adverse effect on our business. Regardless of outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors.

ITEM 1A. RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the risks described below, as well as the other information in this Quarterly Report on Form 10-Q, including our financial statements and the related notes and the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations." The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations and growth prospects. In such an event, the market price of our common stock could decline and you may lose all or part of your investment. Additional risks and uncertainties not presently known to us or that we currently deem immaterial also may impair our business operations and the market price of our common stock. The risk factors set forth below are substantially the same as the risk factors included in our Annual Report on Form 10-K filed with the Securities and Exchange Commission on March 19, 2018.

Risks Related to Our Business, Financial Condition and Capital Requirements

We are in the early stages of clinical drug development and have a very limited operating history and no products approved for commercial sale, which may make it difficult to evaluate our current business and predict our future success and viability.

We are an early clinical-stage biopharmaceutical company with a limited operating history, focused on developing therapeutics for neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis ("ALS"). We commenced operations in May 2015, have no products approved for commercial sale and have not generated any product revenue. Drug development is a highly uncertain undertaking and involves a substantial degree of risk. We have recently initiated clinical trials for our LRRK2 and RIPK1 core programs and have not initiated clinical trials for any of our other current product candidates. To date, we have not initiated or completed a pivotal clinical trial, obtained marketing approval for any product candidates, manufactured a commercial scale product, or arranged for a third party to do so on our behalf, or conducted sales and marketing activities necessary for successful product commercialization. Our short operating history as a company makes any assessment of our future success and viability subject to significant uncertainty. We will encounter risks and difficulties frequently experienced by early-stage biopharmaceutical companies in rapidly evolving fields, and we have not yet demonstrated an ability to successfully overcome such risks and difficulties. If we do not address these risks and difficulties successfully, our business will suffer.

We have incurred significant net losses in each period since our inception and anticipate that we will continue to incur net losses for the foreseeable future.

We have incurred net losses in each reporting period since our inception, including net losses of \$35.4 million and \$113.8 million for the three and nine months ended September 30, 2018, and \$21.8 million and \$65.3 million for the three and nine months ended September 30, 2017, respectively. As of September 30, 2018, we had an accumulated deficit of \$305.5 million.

We have invested significant financial resources in research and development activities, including for our preclinical and clinical product candidates and our BBB platform technology. We do not expect to generate revenue from product sales for several years, if at all. The amount of our future net losses will depend, in part, on the level of our future expenditures and our ability to generate revenue. Moreover, our net losses may fluctuate significantly from quarter to quarter and year to year, such that a period-to-period comparison of our results of operations may not be a good indication of our future performance.

We expect to continue to incur significant expenses and increasingly higher operating losses for the foreseeable future. We anticipate that our expenses will increase substantially if and as we:

- continue our research and discovery activities;
- progress our current and any future product candidates through preclinical and clinical development;
- initiate and conduct additional preclinical, clinical or other studies for our product candidates;
- work with our contract manufacturers to scale up the manufacturing processes for our product candidates or, in the future, establish and operate a manufacturing facility;
- change or add additional contract manufacturers or suppliers;
- seek regulatory approvals and marketing authorizations for our product candidates;
- establish sales, marketing and distribution infrastructure to commercialize any products for which we obtain approval;

[Table of Contents](#)

- acquire or in-license product candidates, intellectual property and technologies;
- make milestone, royalty or other payments due under any license or collaboration agreements;
- obtain, maintain, protect and enforce our intellectual property portfolio, including intellectual property obtained through license agreements;
- attract, hire and retain qualified personnel;
- provide additional internal infrastructure to support our continued research and development operations and any planned commercialization efforts in the future;
- experience any delays or encounter other issues related to our operations;
- meet the requirements and demands of being a public company; and
- defend against any product liability claims or other lawsuits related to our products.

Our prior losses and expected future losses have had and will continue to have an adverse effect on our stockholders' equity and working capital. In any particular quarter or quarters, our operating results could be below the expectations of securities analysts or investors, which could cause our stock price to decline.

Drug development is a highly uncertain undertaking and involves a substantial degree of risk. We have never generated any revenue from product sales, and we may never generate product revenue or be profitable.

We have no products approved for commercial sale and have not generated any revenue from product sales. We do not anticipate generating any revenue from product sales until after we have successfully completed clinical development and received regulatory approval for the commercial sale of a product candidate, if ever.

Our ability to generate revenue and achieve profitability depends significantly on many factors, including:

- successfully completing research and preclinical and clinical development of our product candidates;
- obtaining regulatory approvals and marketing authorizations for product candidates for which we successfully complete clinical development and clinical trials;
- developing a sustainable and scalable manufacturing process for our product candidates, including those that utilize our BBB platform technology, as well as establishing and maintaining commercially viable supply relationships with third parties that can provide adequate products and services to support clinical activities and commercial demand of our product candidates;
- identifying, assessing, acquiring and/or developing new product candidates;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter;
- launching and successfully commercializing product candidates for which we obtain regulatory and marketing approval, either by collaborating with a partner or, if launched independently, by establishing a sales, marketing and distribution infrastructure;

[Table of Contents](#)

- obtaining and maintaining an adequate price for our product candidates, both in the United States and in foreign countries where our products are commercialized;
- obtaining adequate reimbursement for our product candidates from payors;
- obtaining market acceptance of our product candidates as viable treatment options;
- addressing any competing technological and market developments;
- maintaining, protecting, expanding and enforcing our portfolio of intellectual property rights, including patents, trade secrets and know-how; and
- attracting, hiring and retaining qualified personnel.

Because of the numerous risks and uncertainties associated with drug development, we are unable to predict the timing or amount of our expenses, or when we will be able to generate any meaningful revenue or achieve or maintain profitability, if ever. In addition, our expenses could increase beyond our current expectations if we are required by the U.S. Food and Drug Administration, or FDA, or foreign regulatory agencies, to perform studies in addition to those that we currently anticipate, or if there are any delays in any of our or our future collaborators' clinical trials or the development of any of our product candidates. Even if one or more of our product candidates is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate and ongoing compliance efforts.

Even if we are able to generate revenue from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations. Revenue from the sale of any product candidate for which regulatory approval is obtained will be dependent, in part, upon the size of the markets in the territories for which we gain regulatory approval, the accepted price for the product, the ability to get reimbursement at any price and whether we own the commercial rights for that territory. If the number of addressable patients is not as significant as we anticipate, the indication approved by regulatory authorities is narrower than we expect, or the reasonably accepted population for treatment is narrowed by competition, physician choice or treatment guidelines, we may not generate significant revenue from sales of such products, even if approved. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis.

Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our pipeline of product candidates or continue our operations and cause a decline in the value of our common stock, all or any of which may adversely affect our viability.

If we fail to obtain additional financing, we may be unable to complete the development and, if approved, commercialization of our product candidates.

Our operations have required substantial amounts of cash since inception. To date, we have financed our operations primarily through the issuance and sale of convertible preferred stock, the proceeds from our IPO and cash proceeds under our Takeda Collaboration Agreement. We are currently advancing three product candidates, DNL201, DNL151 and DNL747, through clinical development and have several other product candidates in preclinical development, as well as early-stage research projects. Developing our product candidates is expensive, and we expect to continue to spend substantial amounts as we fund our early-stage research projects, continue preclinical development of our seed programs and, in particular, advance our core programs through preclinical development and clinical trials. Even if we are successful in developing our product candidates, obtaining regulatory approvals and launching and commercializing any product candidate will require substantial additional funding.

[Table of Contents](#)

As of September 30, 2018, we had \$517.1 million in cash, cash equivalents and marketable securities. We believe that our existing cash, cash equivalents and marketable securities will be sufficient to fund our projected operations through at least the next 12 months. Our estimate as to how long we expect our existing cash, cash equivalents and marketable securities to be available to fund our operations is based on assumptions that may be proved inaccurate, and we could use our available capital resources sooner than we currently expect. In addition, changing circumstances may cause us to increase our spending significantly faster than we currently anticipate, and we may need to spend more money than currently expected because of circumstances beyond our control. We may need to raise additional funds sooner than we anticipate if we choose to expand more rapidly than we presently anticipate.

We will require additional capital for the further development and, if approved, commercialization of our product candidates. Additional capital may not be available when we need it, on terms acceptable to us or at all. We have no committed source of additional capital. If adequate capital is not available to us on a timely basis, we may be required to significantly delay, scale back or discontinue our research and development programs or the commercialization of any product candidates, if approved, or be unable to continue or expand our operations or otherwise capitalize on our business opportunities, as desired, which could materially affect our business, financial condition and results of operations and cause the price of our common stock to decline.

Due to the significant resources required for the development of our programs, and depending on our ability to access capital, we must prioritize development of certain product candidates. Moreover, we may expend our limited resources on programs that do not yield a successful product candidate and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Our current total portfolio consists of thirteen programs. We designate certain programs as core programs and others as seed programs. Together, these programs require significant capital investment. We currently have eight core programs and five seed programs which are at various stages of research, discovery, preclinical and early clinical development. We seek to maintain a process of prioritization and resource allocation to maintain an optimal balance between aggressively advancing lead programs and ensuring replenishment of our portfolio. We regularly review the designation of each program as core or seed, and terminate those programs which do not meet our development criteria, which we have done with nine programs in the past two years.

Due to the significant resources required for the development of our programs, we must focus our programs on specific diseases and disease pathways and decide which product candidates to pursue and advance and the amount of resources to allocate to each. Our decisions concerning the allocation of research, development, collaboration, management and financial resources toward particular product candidates or therapeutic areas may not lead to the development of any viable commercial product and may divert resources away from better opportunities. Similarly, our potential decisions to delay, terminate or collaborate with third parties in respect of certain programs may subsequently also prove to be suboptimal and could cause us to miss valuable opportunities. If we make incorrect determinations regarding the viability or market potential of any of our programs or product candidates or misread trends in the biopharmaceutical industry, in particular for neurodegenerative diseases, our business, financial condition and results of operations could be materially adversely affected. As a result, we may fail to capitalize on viable commercial products or profitable market opportunities, be required to forego or delay pursuit of opportunities with other product candidates or other diseases and disease pathways that may later prove to have greater commercial potential than those we choose to pursue, or relinquish valuable rights to such product candidates through collaboration, licensing or other royalty arrangements in cases in which it would have been advantageous for us to invest additional resources to retain sole development and commercialization rights.

Risks Related to the Discovery, Development and Commercialization of Our Product Candidates

Research and development of biopharmaceutical products is inherently risky. We are heavily dependent on the successful development of our BBB platform technology and the product candidates currently in our core programs, which are in the early stages of preclinical and clinical development. We cannot give any assurance that any of our product candidates will receive regulatory, including marketing, approval, which is necessary before they can be commercialized.

We are at an early stage of development of the product candidates currently in our programs and are further developing our BBB platform technology. To date, we have invested substantially all of our efforts and financial resources to identify, acquire intellectual property for, and develop our BBB platform technology and our programs, including conducting preclinical studies and early-stage clinical trials in our core programs, and providing general and administrative support for these operations. Our future success is dependent on our ability to successfully develop, obtain regulatory approval for, and then successfully commercialize our product candidates, and we may fail to do so for many reasons, including the following:

- our product candidates may not successfully complete preclinical studies or clinical trials;
- our drug delivery platform technology designed to deliver large molecule therapeutics across the BBB may not be clinically viable;
- a product candidate may on further study be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;
- our competitors may develop therapeutics that render our product candidates obsolete or less attractive;
- our competitors may develop platform technologies to deliver large molecule therapeutics across the BBB that render our platform technology obsolete or less attractive;
- the product candidates and BBB platform technology that we develop may not be sufficiently covered by intellectual property for which we hold exclusive rights;
- the product candidates and BBB platform technology that we develop may be covered by third parties' patents or other intellectual property or exclusive rights;
- the market for a product candidate may change so that the continued development of that product candidate is no longer reasonable or commercially attractive;
- a product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all;
- if a product candidate obtains regulatory approval, we may be unable to establish sales and marketing capabilities, or successfully market such approved product candidate, to gain market acceptance; and
- a product candidate may not be accepted as safe and effective by patients, the medical community or third-party payors, if applicable.

If any of these events occur, we may be forced to abandon our development efforts for a program or programs, which would have a material adverse effect on our business and could potentially cause us to cease operations.

[Table of Contents](#)

We may not be successful in our efforts to further develop our BBB platform technology and current product candidates. We are not permitted to market or promote any of our product candidates before we receive regulatory approval from the FDA or comparable foreign regulatory authorities, and we may never receive such regulatory approval for any of our product candidates. Each of our product candidates is in the early stages of development and will require significant additional clinical development, management of preclinical, clinical, and manufacturing activities, regulatory approval, adequate manufacturing supply, a commercial organization, and significant marketing efforts before we generate any revenue from product sales, if at all.

We have never completed a clinical development program. In the past two years, we have discontinued the development of three programs prior to completion of preclinical development because we did not believe they met our criteria for potential clinical success. We currently have one product candidate, DNL201, for which recruitment has commenced for the Phase 1b clinical study in Parkinson's disease patients with and without the genetic LRRK2 mutation, with the first patient expected to be dosed in late 2018, and two product candidates, DNL151 and DNL747, in Phase 1 clinical trials in healthy volunteers in the Netherlands. None of our product candidates have advanced into late-stage development or a pivotal clinical trial and it may be years before any such trial is initiated, if at all. Further, we cannot be certain that any of our product candidates will be successful in clinical trials. For instance, in 2016, we initiated a Phase 1 clinical trial in a former RIPK1 inhibitor product candidate, DNL104, which we subsequently discontinued based on liver test abnormalities in some clinical trial healthy volunteer participants. We may in the future advance product candidates into clinical trials and terminate such trials prior to their completion.

If any of our product candidates successfully complete clinical trials, we generally plan to seek regulatory approval to market our product candidates in the United States, the European Union, or EU, and in additional foreign countries where we believe there is a viable commercial opportunity. We have never commenced, compiled or submitted an application seeking regulatory approval to market any product candidate. We may never receive regulatory approval to market any product candidates even if such product candidates successfully complete clinical trials, which would adversely affect our viability. To obtain regulatory approval in countries outside the United States, we must comply with numerous and varying regulatory requirements of such other countries regarding safety, efficacy, chemistry, manufacturing and controls, clinical trials, commercial sales, pricing, and distribution of our product candidates. We may also rely on our collaborators or partners to conduct the required activities to support an application for regulatory approval, and to seek approval, for one or more of our product candidates. We cannot be sure that our collaborators or partners will conduct these activities or do so within the timeframe we desire. Even if we (or our collaborators or partners) are successful in obtaining approval in one jurisdiction, we cannot ensure that we will obtain approval in any other jurisdictions. If we are unable to obtain approval for our product candidates in multiple jurisdictions, our revenue and results of operations could be negatively affected.

Even if we receive regulatory approval to market any of our product candidates, whether for the treatment of neurodegenerative diseases or other diseases, we cannot assure you that any such product candidate will be successfully commercialized, widely accepted in the marketplace or more effective than other commercially available alternatives.

Investment in biopharmaceutical product development involves significant risk that any product candidate will fail to demonstrate adequate efficacy or an acceptable safety profile, gain regulatory approval, and become commercially viable. We cannot provide any assurance that we will be able to successfully advance any of our product candidates through the development process or, if approved, successfully commercialize any of our product candidates.

We may not be successful in our efforts to continue to create a pipeline of product candidates or to develop commercially successful products. If we fail to successfully identify and develop additional product candidates, our commercial opportunity may be limited.

[Table of Contents](#)

One of our strategies is to identify and pursue clinical development of additional product candidates. We currently have five seed programs, all of which are in the research, discovery and preclinical stages of development. Identifying, developing, obtaining regulatory approval and commercializing additional product candidates for the treatment of neurodegenerative diseases will require substantial additional funding and is prone to the risks of failure inherent in drug development. We cannot provide you any assurance that we will be able to successfully identify or acquire additional product candidates, advance any of these additional product candidates through the development process, successfully commercialize any such additional product candidates, if approved, or assemble sufficient resources to identify, acquire, develop or, if approved, commercialize additional product candidates. If we are unable to successfully identify, acquire, develop and commercialize additional product candidates, our commercial opportunity may be limited.

We have concentrated our research and development efforts on the treatment of neurodegenerative diseases, a field that has seen limited success in drug development. Further, our product candidates are based on new approaches and novel technology, which makes it difficult to predict the time and cost of product candidate development and subsequently obtaining regulatory approval.

We have focused our research and development efforts on addressing neurodegenerative diseases. Collectively, efforts by biopharmaceutical companies in the field of neurodegenerative diseases have seen limited successes in drug development. There are few effective therapeutic options available for patients with Alzheimer's disease, Parkinson's disease, ALS and other neurodegenerative diseases. Our future success is highly dependent on the successful development of our BBB platform technology and our product candidates for treating neurodegenerative diseases. Developing and, if approved, commercializing our product candidates for treatment of neurodegenerative diseases subjects us to a number of challenges, including engineering product candidates to cross the BBB to enable optimal concentration of the therapeutic in the brain and obtaining regulatory approval from the FDA and other regulatory authorities who have only a limited set of precedents to rely on.

Our approach to the treatment of neurodegenerative diseases aims to identify and select targets with a genetic link to neurodegenerative diseases, identify and develop molecules that engage the intended target, identify and develop biomarkers, which are biological molecules found in blood, other bodily fluids or tissues that are signs of a normal or abnormal process or of a condition or disease, to select the right patient population and demonstrate target engagement, pathway engagement and impact on disease progression of our molecules, and engineer our molecules to cross the BBB and act directly in the brain. This strategy may not prove to be successful. We may not be able to discover, develop and utilize biomarkers to demonstrate target engagement, pathway engagement and the impact on disease progression of our molecules. We cannot be sure that our approach will yield satisfactory therapeutic products that are safe and effective, scalable, or profitable. Moreover, public perception of drug safety issues, including adoption of new therapeutics or novel approaches to treatment, may adversely influence the willingness of subjects to participate in clinical trials, or if approved, of physicians to subscribe to novel treatments.

We may encounter substantial delays in our clinical trials, or may not be able to conduct or complete our clinical trials on the timelines we expect, if at all.

Clinical testing is expensive, time consuming, and subject to uncertainty. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. We cannot be sure that submission of an investigational new drug application, or IND, or a clinical trial application, or CTA, will result in the FDA or European Medicines Agency, or EMA, as applicable, allowing clinical trials to begin in a timely manner, if at all. Moreover, even if these trials begin, issues may arise that could suspend or terminate such clinical trials. A failure of one or more clinical trials can occur at any stage of testing, and our future clinical trials may not be successful. Events that may prevent successful or timely initiation or completion of clinical trials include:

[Table of Contents](#)

- inability to generate sufficient preclinical, toxicology, or other *in vivo* or *in vitro* data to support the initiation or continuation of clinical trials;
- delays in confirming target engagement, patient selection or other relevant biomarkers to be utilized in preclinical and clinical product candidate development;
- delays in reaching a consensus with regulatory agencies on study design;
- delays in reaching agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical trial sites;
- delays in identifying, recruiting and training suitable clinical investigators;
- delays in obtaining required Institutional Review Board, or IRB, approval at each clinical trial site;
- imposition of a temporary or permanent clinical hold by regulatory agencies for a number of reasons, including after review of an IND or amendment, CTA or amendment, or equivalent application or amendment; as a result of a new safety finding that presents unreasonable risk to clinical trial participants; a negative finding from an inspection of our clinical trial operations or study sites; developments on trials conducted by competitors for related technology that raises FDA or EMA concerns about risk to patients of the technology broadly; or if the FDA or EMA finds that the investigational protocol or plan is clearly deficient to meet its stated objectives;
- delays in identifying, recruiting and enrolling suitable patients to participate in our clinical trials, and delays caused by patients withdrawing from clinical trials or failing to return for post-treatment follow-up;
- difficulty collaborating with patient groups and investigators;
- failure by our CROs, other third parties, or us to adhere to clinical trial requirements;
- failure to perform in accordance with the FDA's or any other regulatory authority's current good clinical practices ("cGCPs") requirements, or applicable EMA or other regulatory guidelines in other countries;
- occurrence of adverse events associated with the product candidate that are viewed to outweigh its potential benefits;
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols;
- changes in the standard of care on which a clinical development plan was based, which may require new or additional trials;
- the cost of clinical trials of our product candidates being greater than we anticipate;
- clinical trials of our product candidates producing negative or inconclusive results, which may result in our deciding, or regulators requiring us, to conduct additional clinical trials or abandon product development programs;
- transfer of manufacturing processes from our academic collaborators to larger-scale facilities operated by a CMO or by us, and delays or failure by our CMOs or us to make any necessary changes to such manufacturing process; and

[Table of Contents](#)

- delays in manufacturing, testing, releasing, validating, or importing/exporting sufficient stable quantities of our product candidates for use in clinical trials or the inability to do any of the foregoing.

Any inability to successfully initiate or complete clinical trials could result in additional costs to us or impair our ability to generate revenue. In addition, if we make manufacturing or formulation changes to our product candidates, we may be required to or we may elect to conduct additional studies to bridge our modified product candidates to earlier versions. Clinical trial delays could also shorten any periods during which our products have patent protection and may allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

We could also encounter delays if a clinical trial is suspended or terminated by us, by the data safety monitoring board for such trial or by the FDA, EMA or any other regulatory authority, or if the IRBs of the institutions in which such trials are being conducted suspend or terminate the participation of their clinical investigators and sites subject to their review. Such authorities may suspend or terminate a clinical trial due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA, EMA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a product candidate, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial.

Our most advanced product candidate, DNL201, has commenced recruitment for the Phase 1b clinical study in Parkinson's disease patients with and without the genetic LRRK2 mutation, with the first patient expected to be dosed in late 2018. This program was previously subject to a partial clinical hold due to preclinical toxicity data. The partial clinical hold was removed in December 2017 based on additional clinical and preclinical data provided to the FDA. Our second and third most advanced product candidates, DNL151 and DNL747, are both currently in Phase 1 clinical trials in healthy volunteers. In the nonclinical safety studies for DNL201, DNL151, and DNL747, toxicities were observed at high doses in rat and/or cynomolgus monkey above doses and exposures that will be tested in the clinic. We cannot assure you that DNL201, DNL151, DNL747 or our other product candidates will not be subject to new, partial or full clinical holds in the future.

We may in the future advance product candidates into clinical trials and terminate such trials prior to their completion, such as we did for DNL104, which could adversely affect our business.

Delays in the completion of any clinical trial of our product candidates will increase our costs, slow down our product candidate development and approval process and delay or potentially jeopardize our ability to commence product sales and generate revenue. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates.

We may encounter difficulties enrolling patients in our clinical trials, and our clinical development activities could thereby be delayed or otherwise adversely affected.

The timely completion of clinical trials in accordance with their protocols depends, among other things, on our ability to enroll a sufficient number of patients who remain in the trial until its conclusion. We may experience difficulties in patient enrollment in our clinical trials for a variety of reasons, including:

- the size and nature of the patient population;
- the patient eligibility criteria defined in the protocol, including biomarker-driven identification and/or certain highly-specific criteria related to stage of disease progression, which may limit the patient populations eligible for our clinical trials to a greater extent than competing clinical trials for the same indication that do not have biomarker-driven patient eligibility criteria;

[Table of Contents](#)

- the size of the study population required for analysis of the trial's primary endpoints;
- the proximity of patients to a trial site;
- the design of the trial;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience;
- competing clinical trials for similar therapies or targeting patient populations meeting our patient eligibility criteria;
- clinicians' and patients' perceptions as to the potential advantages and side effects of the product candidate being studied in relation to other available therapies and product candidates;
- our ability to obtain and maintain patient consents; and
- the risk that patients enrolled in clinical trials will not complete such trials, for any reason.

Our clinical trials may fail to demonstrate substantial evidence of the safety and efficacy of our product candidates, which would prevent, delay or limit the scope of regulatory approval and commercialization.

Before obtaining regulatory approvals for the commercial sale of any of our product candidates, we must demonstrate through lengthy, complex and expensive preclinical studies and clinical trials that our product candidates are both safe and effective for use in each target indication. For those product candidates that are subject to regulation as biological drug products, we will need to demonstrate that they are safe, pure, and potent for use in their target indications. Each product candidate must demonstrate an adequate risk versus benefit profile in its intended patient population and for its intended use.

Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. The results of preclinical studies of our product candidates may not be predictive of the results of early-stage or later-stage clinical trials, and results of early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials. The results of clinical trials in one set of patients or disease indications may not be predictive of those obtained in another. In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, changes in and adherence to the dosing regimen and other clinical trial protocols and the rate of dropout among clinical trial participants. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy profile despite having progressed through preclinical studies and initial clinical trials. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or unacceptable safety issues, notwithstanding promising results in earlier trials. This is particularly true in neurodegenerative diseases, where failure rates historically have been higher than in many other disease areas. Most product candidates that begin clinical trials are never approved by regulatory authorities for commercialization.

We have limited experience in designing clinical trials and may be unable to design and execute a clinical trial to support marketing approval. We cannot be certain that our current clinical trials or any other future clinical trials will be successful. Additionally, any safety concerns observed in any one of our clinical trials in our targeted indications could limit the prospects for regulatory approval of our product candidates in those and other indications, which could have a material adverse effect on our business, financial condition and results of operations.

[Table of Contents](#)

In addition, even if such clinical trials are successfully completed, we cannot guarantee that the FDA or foreign regulatory authorities will interpret the results as we do, and more trials could be required before we submit our product candidates for approval. To the extent that the results of the trials are not satisfactory to the FDA or foreign regulatory authorities for support of a marketing application, we may be required to expend significant resources, which may not be available to us, to conduct additional trials in support of potential approval of our product candidates. Even if regulatory approval is secured for any of our product candidates, the terms of such approval may limit the scope and use of our product candidate, which may also limit its commercial potential.

We face significant competition in an environment of rapid technological and scientific change, and there is a possibility that our competitors may achieve regulatory approval before us or develop therapies that are safer, more advanced or more effective than ours, which may negatively impact our ability to successfully market or commercialize any product candidates we may develop and ultimately harm our financial condition.

The development and commercialization of new drug products is highly competitive. Moreover, the neurodegenerative field is characterized by strong and increasing competition, and a strong emphasis on intellectual property. We may face competition with respect to any product candidates that we seek to develop or commercialize in the future from major pharmaceutical companies, specialty pharmaceutical companies, and biotechnology companies worldwide. Potential competitors also include academic institutions, government agencies, and other public and private research organizations that conduct research, seek patent protection, and establish collaborative arrangements for research, development, manufacturing, and commercialization.

There are a number of large pharmaceutical and biotechnology companies that are currently pursuing the development of products for the treatment of the neurodegenerative disease indications for which we have research programs, including Alzheimer's disease, Parkinson's disease and ALS. Companies that we are aware are developing therapeutics in the neurodegenerative disease area include large companies with significant financial resources, such as AbbVie, AstraZeneca, Biogen, Celgene, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Novartis, Roche, Sanofi and Takeda. In addition to competition from other companies targeting neurodegenerative indications, any products we may develop may also face competition from other types of therapies, such as gene-editing therapies.

Many of our current or potential competitors, either alone or with their strategic partners, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals, and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient, or are less expensive than any products that we may develop. Furthermore, currently approved products could be discovered to have application for treatment of neurodegenerative disease indications, which could give such products significant regulatory and market timing advantages over any of our product candidates. Our competitors also may obtain FDA, EMA or other regulatory approval for their products more rapidly than we may obtain approval for ours and may obtain orphan product exclusivity from the FDA for indications our product candidates are targeting, which could result in our competitors establishing a strong market position before we are able to enter the market. Additionally, products or technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing any product candidates we may develop against competitors.

[Table of Contents](#)

In addition, we could face litigation or other proceedings with respect to the scope, ownership, validity and/or enforceability of our patents relating to our competitors' products and our competitors may allege that our products infringe, misappropriate or otherwise violate their intellectual property. The availability of our competitors' products could limit the demand, and the price we are able to charge, for any products that we may develop and commercialize. See "Risks Related to Our Intellectual Property."

The manufacture of our product candidates, particularly those that utilize our BBB platform technology, is complex and we may encounter difficulties in production. If we or any of our third-party manufacturers encounter such difficulties, or fail to meet rigorously enforced regulatory standards, our ability to provide supply of our product candidates for clinical trials or our products for patients, if approved, could be delayed or stopped, or we may be unable to maintain a commercially viable cost structure.

The processes involved in manufacturing our drug and biological product candidates, particularly those that utilize our BBB platform technology, are complex, expensive, highly-regulated and subject to multiple risks. Additionally, the manufacture of biologics involves complex processes, including developing cells or cell systems to produce the biologic, growing large quantities of such cells, and harvesting and purifying the biologic produced by them. As a result, the cost to manufacture a biologic is generally far higher than traditional small molecule chemical compounds, and the biologics manufacturing process is less reliable and is difficult to reproduce. Manufacturing biologics is highly susceptible to product loss due to contamination, equipment failure, improper installation or operation of equipment, vendor or operator error, inconsistency in yields, variability in product characteristics and difficulties in scaling the production process. Even minor deviations from normal manufacturing processes could result in reduced production yields, product defects and other supply disruptions. Further, as product candidates are developed through preclinical studies to late-stage clinical trials towards approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods, are altered along the way in an effort to optimize processes and results. Such changes carry the risk that they will not achieve these intended objectives, and any of these changes could cause our product candidates to perform differently and affect the results of planned clinical trials or other future clinical trials.

In order to conduct clinical trials of our product candidates, or supply commercial products, if approved, we will need to manufacture them in small and large quantities. Our manufacturing partners may be unable to successfully increase the manufacturing capacity for any of our product candidates in a timely or cost-effective manner, or at all. In addition, quality issues may arise during scale-up activities. If our manufacturing partners are unable to successfully scale up the manufacture of our product candidates in sufficient quality and quantity, the development, testing and clinical trials of that product candidate may be delayed or become infeasible, and regulatory approval or commercial launch of any resulting product may be delayed or not obtained, which could significantly harm our business. The same risks would apply to our internal manufacturing facilities, should we in the future decide to build internal manufacturing capacity. In addition, building internal manufacturing capacity would carry significant risks in terms of being able to plan, design and execute on a complex project to build manufacturing facilities in a timely and cost-efficient manner.

[Table of Contents](#)

In addition, the manufacturing process for any products that we may develop is subject to FDA, EMA and foreign regulatory authority approval processes, and continuous oversight, and we will need to contract with manufacturers who can meet all applicable FDA, EMA and foreign regulatory authority requirements, including complying with current good manufacturing practices ("cGMPs"), on an ongoing basis. If we or our third-party manufacturers are unable to reliably produce products to specifications acceptable to the FDA, EMA or other regulatory authorities, we may not obtain or maintain the approvals we need to commercialize such products. Even if we obtain regulatory approval for any of our product candidates, there is no assurance that either we or our CMOs will be able to manufacture the approved product to specifications acceptable to the FDA, EMA or other regulatory authorities, to produce it in sufficient quantities to meet the requirements for the potential launch of the product, or to meet potential future demand. Any of these challenges could delay completion of clinical trials, require bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our product candidate, impair commercialization efforts, increase our cost of goods, and have an adverse effect on our business, financial condition, results of operations and growth prospects.

If, in the future, we are unable to establish sales and marketing capabilities or enter into agreements with third parties to sell and market any product candidates we may develop, we may not be successful in commercializing those product candidates if and when they are approved.

We do not have a sales or marketing infrastructure and have no experience in the sale, marketing, or distribution of pharmaceutical products. To achieve commercial success for any approved product for which we retain sales and marketing responsibilities, we must either develop a sales and marketing organization or outsource these functions to third parties. In the future, we may choose to build a focused sales, marketing, and commercial support infrastructure to sell, or participate in sales activities with our collaborators for, some of our product candidates if and when they are approved.

There are risks involved with both establishing our own commercial capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force or reimbursement specialists is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing and other commercialization capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our commercialization personnel.

Factors that may inhibit our efforts to commercialize any approved product on our own include:

- our inability to recruit and retain adequate numbers of effective sales, marketing, reimbursement, customer service, medical affairs, and other support personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future approved products;
- the inability of reimbursement professionals to negotiate arrangements for formulary access, reimbursement, and other acceptance by payors;
- the inability to price our products at a sufficient price point to ensure an adequate and attractive level of profitability;
- restricted or closed distribution channels that make it difficult to distribute our products to segments of the patient population;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent commercialization organization.

[Table of Contents](#)

If we enter into arrangements with third parties to perform sales, marketing, commercial support, and distribution services, our product revenue or the profitability of product revenue may be lower than if we were to market and sell any products we may develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to commercialize our product candidates or may be unable to do so on terms that are favorable to us. We may have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. If we do not establish commercialization capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates if approved.

Even if any product candidates we develop receive marketing approval, they may fail to achieve the degree of market acceptance by physicians, patients, healthcare payors, and others in the medical community necessary for commercial success.

The commercial success of any of our product candidates will depend upon its degree of market acceptance by physicians, patients, third-party payors, and others in the medical community. Even if any product candidates we may develop receive marketing approval, they may nonetheless fail to gain sufficient market acceptance by physicians, patients, healthcare payors, and others in the medical community. The degree of market acceptance of any product candidates we may develop, if approved for commercial sale, will depend on a number of factors, including:

- the efficacy and safety of such product candidates as demonstrated in pivotal clinical trials and published in peer-reviewed journals;
- the potential and perceived advantages compared to alternative treatments;
- the ability to offer our products for sale at competitive prices;
- the ability to offer appropriate patient access programs, such as co-pay assistance;
- the extent to which physicians recommend our products to their patients;
- convenience and ease of dosing and administration compared to alternative treatments;
- the clinical indications for which the product candidate is approved by FDA, EMA or other regulatory agencies;
- product labeling or product insert requirements of the FDA, EMA or other comparable foreign regulatory authorities, including any limitations, contraindications or warnings contained in a product's approved labeling;
- restrictions on how the product is distributed;
- the timing of market introduction of competitive products;
- publicity concerning our products or competing products and treatments;
- the strength of marketing and distribution support;
- sufficient third-party coverage or reimbursement; and
- the prevalence and severity of any side effects.

If any product candidates we develop do not achieve an adequate level of acceptance, we may not generate significant product revenue, and we may not become profitable.

Even if we are able to commercialize any product candidates, such products may become subject to unfavorable pricing regulations, third-party reimbursement practices, or healthcare reform initiatives, which would harm our business.

The regulations that govern marketing approvals, pricing, and reimbursement for new drugs vary widely from country to country. In the United States, recently enacted legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay our commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenue we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if any product candidates we may develop obtain marketing approval.

Our ability to successfully commercialize any products that we may develop also will depend in part on the extent to which reimbursement for these products and related treatments will be available from government health administration authorities, private health insurers, and other organizations. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels. A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. Government authorities currently impose mandatory discounts for certain patient groups, such as Medicare, Medicaid and Veterans Affairs, or VA, hospitals, and may seek to increase such discounts at any time. Future regulation may negatively impact the price of our products, if approved. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. We cannot be sure that reimbursement will be available for any product candidate that we commercialize and, if reimbursement is available, the level of reimbursement. Reimbursement may impact the demand for, or the price of, any product candidate for which we obtain marketing approval. In order to get reimbursement, physicians may need to show that patients have superior treatment outcomes with our products compared to standard of care drugs, including lower-priced generic versions of standard of care drugs. If reimbursement is not available or is available only to limited levels, we may not be able to successfully commercialize any product candidate for which we obtain marketing approval. In the United States, no uniform policy of coverage and reimbursement for products exists among third-party payors and coverage and reimbursement levels for products can differ significantly from payor to payor. As a result, the coverage determination process is often a time consuming and costly process that may require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

[Table of Contents](#)

There may be significant delays in obtaining reimbursement for newly approved drugs, and coverage may be more limited than the purposes for which the medicine is approved by the FDA, EMA or other comparable foreign regulatory authorities. Moreover, eligibility for reimbursement does not imply that any drug will be paid for in all cases or at a rate that covers our costs, including research, development, manufacture, sale, and distribution. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. Net prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors and by any future relaxation of laws that presently restrict imports of drugs from countries where they may be sold at lower prices than in the United States. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement policies. Our inability to promptly obtain coverage and profitable payment rates from both government-funded and private payors for any approved products we may develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize product candidates, and our overall financial condition.

If any of our product candidates that are small molecules obtain regulatory approval, additional competitors could enter the market with generic versions of such drugs, which may result in a material decline in sales of affected products.

Under the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, a pharmaceutical manufacturer may file an abbreviated new drug application, or ANDA, seeking approval of a generic copy of an approved, small molecule innovator product. Under the Hatch-Waxman Act, a manufacturer may also submit a new drug application, or NDA, under section 505(b)(2) that references the FDA's prior approval of the small molecule innovator product. A 505(b)(2) NDA product may be for a new or improved version of the original innovator product. The Hatch-Waxman Act also provides for certain periods of regulatory exclusivity, which preclude FDA approval (or in some circumstances, FDA filing and reviewing) of an ANDA or 505(b)(2) NDA. These include, subject to certain exceptions, the period during which an FDA-approved drug is subject to orphan drug exclusivity. In addition to the benefits of regulatory exclusivity, an innovator NDA holder may have patents claiming the active ingredient, product formulation or an approved use of the drug, which would be listed with the product in the FDA publication, "Approved Drug Products with Therapeutic Equivalence Evaluations," known as the "Orange Book." If there are patents listed in the Orange Book, a generic or 505(b)(2) applicant that seeks to market its product before expiration of the patents must include in the ANDA a "Paragraph IV certification," challenging the validity or enforceability of, or claiming non-infringement of, the listed patent or patents. Notice of the certification must be given to the innovator, too, and if within 45 days of receiving notice the innovator sues to protect its patents, approval of the ANDA is stayed for 30 months, or as lengthened or shortened by the court.

Accordingly, if any of our small molecule product candidates are approved, competitors could file ANDAs for generic versions of our small molecule drug products or 505(b)(2) NDAs that reference our small molecule drug products, respectively. If there are patents listed for our small molecule drug products in the Orange Book, those ANDAs and 505(b)(2) NDAs would be required to include a certification as to each listed patent indicating whether the ANDA applicant does or does not intend to challenge the patent. We cannot predict which, if any, patents in our current portfolio or patents we may obtain in the future will be eligible for listing in the Orange Book, how any generic competitor would address such patents, whether we would sue on any such patents, or the outcome of any such suit.

We may not be successful in securing or maintaining proprietary patent protection for products and technologies we develop or license. Moreover, if any of our owned or in-licensed patents that are listed in the Orange Book are successfully challenged by way of a Paragraph IV certification and subsequent litigation, the affected product could immediately face generic competition and its sales would likely decline rapidly and materially. Should sales decline, we may have to write off a portion or all of the intangible assets associated with the affected product and our results of operations and cash flows could be materially and adversely affected. See "Risks Related to Our Intellectual Property."

Our biologic, or large molecule, product candidates for which we intend to seek approval may face competition sooner than anticipated.

Even if we are successful in achieving regulatory approval to commercialize a product candidate faster than our competitors, our large molecule product candidates may face competition from biosimilar products. In the United States, our large molecule product candidates are regulated by the FDA as biologic products and we intend to seek approval for these product candidates pursuant to the biologics license application, or BLA, pathway. The Biologics Price Competition and Innovation Act of 2009, or BPCIA, created an abbreviated pathway for the approval of biosimilar and interchangeable biologic products. The abbreviated regulatory pathway establishes legal authority for the FDA to review and approve biosimilar biologics, including the possible designation of a biosimilar as “interchangeable” based on its similarity to an existing brand product. Under the BPCIA, an application for a biosimilar product cannot be approved by the FDA until 12 years after the original branded product was approved under a BLA. The law is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation, and meaning are subject to uncertainty. While it is uncertain when such processes intended to implement BPCIA may be fully adopted by the FDA, any such processes could have a material adverse effect on the future commercial prospects for our large molecule product candidates.

We believe that any of our large molecule product candidates approved as a biologic product under a BLA should qualify for the 12-year period of exclusivity. However, there is a risk that this exclusivity could be shortened due to congressional action or otherwise, or that the FDA will not consider our product candidates to be reference products for competing products, potentially creating the opportunity for generic competition sooner than anticipated. Moreover, the extent to which a biosimilar product, once approved, will be substituted for any one of our reference products in a way that is similar to traditional generic substitution for non-biologic products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing. In addition, a competitor could decide to forego the biosimilar approval path and submit a full BLA after completing its own preclinical studies and clinical trials. In such cases, any exclusivity to which we may be eligible under the BPCIA would not prevent the competitor from marketing its product as soon as it is approved.

In Europe, the European Commission has granted marketing authorizations for several biosimilar products pursuant to a set of general and product class-specific guidelines for biosimilar approvals issued over the past few years. In Europe, a competitor may reference data supporting approval of an innovative biological product, but will not be able to get it on the market until 10 years after the time of approval of the innovative product. This 10-year marketing exclusivity period will be extended to 11 years if, during the first eight of those 10 years, the marketing authorization holder obtains an approval for one or more new therapeutic indications that bring significant clinical benefits compared with existing therapies. In addition, companies may be developing biosimilar products in other countries that could compete with our products, if approved.

If competitors are able to obtain marketing approval for biosimilars referencing our large molecule product candidates, if approved, such products may become subject to competition from such biosimilars, with the attendant competitive pressure and potential adverse consequences. Such competitive products may be able to immediately compete with us in each indication for which our product candidates may have received approval.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.

[Table of Contents](#)

We face an inherent risk of product liability as a result of the clinical testing of our product candidates and will face an even greater risk when and if we commercialize any products. For example, we may be sued if our product candidates cause or are perceived to cause injury or are found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit testing and commercialization of our product candidates. Even successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased or interrupted demand for our products;
- injury to our reputation;
- withdrawal of clinical trial participants and inability to continue clinical trials;
- initiation of investigations by regulators;
- costs to defend the related litigation;
- a diversion of management's time and our resources;
- substantial monetary awards to trial participants or patients;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- exhaustion of any available insurance and our capital resources;
- the inability to commercialize any product candidate; and
- a decline in our share price.

Our inability to obtain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of products we develop, alone or with collaborators. Our insurance policies may have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We may have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts. Even if our agreements with any future corporate collaborators entitle us to indemnification against losses, such indemnification may not be available or adequate should any claim arise.

Risks Related to Regulatory Approval and Other Legal Compliance Matters

The regulatory approval processes of the FDA, EMA and comparable foreign regulatory authorities are lengthy, time consuming, and inherently unpredictable. If we are ultimately unable to obtain regulatory approval for our product candidates, we will be unable to generate product revenue and our business will be substantially harmed.

[Table of Contents](#)

The time required to obtain approval by the FDA, EMA and comparable foreign regulatory authorities is unpredictable, typically takes many years following the commencement of clinical trials, and depends upon numerous factors, including the type, complexity and novelty of the product candidates involved. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions, which may cause delays in the approval or the decision not to approve an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. Moreover, the FDA, EMA or other regulatory authorities may fail to approve companion diagnostics that we contemplate using with our therapeutic product candidates. We have not submitted for, or obtained regulatory approval for any product candidate, and it is possible that none of our existing product candidates or any product candidates we may seek to develop in the future will ever obtain regulatory approval.

Applications for our product candidates could fail to receive regulatory approval in an initial or subsequent indication for many reasons, including but not limited to the following:

- the FDA, EMA or comparable foreign regulatory authorities may disagree with the design, implementation or results of our clinical trials;
- the FDA, EMA or comparable foreign regulatory authorities may determine that our product candidates are not safe and effective, only moderately effective or have undesirable or unintended side effects, toxicities or other characteristics that preclude our obtaining marketing approval or prevent or limit commercial use;
- the population studied in the clinical program may not be sufficiently broad or representative to assure efficacy and safety in the full population for which we seek approval;
- we may be unable to demonstrate to the FDA or comparable foreign regulatory authorities that a product candidate's risk-benefit ratio when compared to the standard of care is acceptable;
- the FDA, EMA or comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials;
- the data collected from clinical trials of our product candidates may not be sufficient to support the submission of an NDA, BLA, or other submission or to obtain regulatory approval in the United States or elsewhere;
- we may be unable to demonstrate to the FDA, EMA or comparable foreign regulatory authorities that a product candidate's risk-benefit ratio for its proposed indication is acceptable;
- the FDA, EMA or comparable foreign regulatory authorities may fail to approve the manufacturing processes, test procedures and specifications, or facilities of third-party manufacturers with which we contract for clinical and commercial supplies; and
- the approval policies or regulations of the FDA, EMA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

This lengthy approval process, as well as the unpredictability of the results of clinical trials, may result in our failing to obtain regulatory approval to market any of our product candidates, which would significantly harm our business, results of operations, and prospects.

Our product candidates may cause undesirable side effects or have other properties that could halt their clinical development, prevent their regulatory approval, limit their commercial potential, or result in significant negative consequences.

[Table of Contents](#)

Adverse events or other undesirable side effects caused by our product candidates could cause us or regulatory authorities to interrupt, delay, or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA, EMA or other comparable foreign regulatory authorities.

Our most advanced product candidates, DNL201, DNL151, and DNL747 are currently our only clinical stage product candidates. In 2017, we initiated Phase 1 clinical trials of DNL201 and DNL151 in healthy volunteers. In its trial, DNL201 achieved its safety, pharmacokinetic, and pharmacodynamic objectives. DNL201 was generally well tolerated with no serious adverse events at doses that achieved high levels of CSF exposure and robust target engagement as measured by two blood based biomarkers of LRRK2 activity. On August 1, 2018, we announced positive results from the DNL201 Phase 1 Healthy Volunteer Study and data from this study was presented at the Michael J Fox Foundation Parkinson's Disease Therapeutic Conference on October 25, 2018. Recruitment has commenced for the Phase 1b clinical study in Parkinson's disease patients with and without the genetic LRRK2 mutation, with the first patient expected to be dosed in late 2018. To date, DNL151 has been well tolerated. We initiated a Phase 1 clinical trial of DNL747 in healthy volunteers in March 2018. Adverse events and other side effects may result from higher dosing, repeated dosing and/or longer-term exposure to DNL201, DNL151 and/or DNL747 and could lead to delays and/or termination of the development of these product candidates.

In 2016, we initiated a Phase 1 clinical trial in a former RIPK1 inhibitor product candidate, DNL104, which we subsequently discontinued based on liver function test abnormalities in some clinical trial healthy volunteer participants.

Drug-related side effects could affect patient recruitment, the ability of enrolled patients to complete the study, and/or result in potential product liability claims. We are required to maintain product liability insurance pursuant to certain of our license agreements. We may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. A successful product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business. In addition, regardless of merit or eventual outcome, product liability claims may result in impairment of our business reputation, withdrawal of clinical trial participants, costs due to related litigation, distraction of management's attention from our primary business, initiation of investigations by regulators, substantial monetary awards to patients or other claimants, the inability to commercialize our product candidates, and decreased demand for our product candidates, if approved for commercial sale.

Additionally, if one or more of our product candidates receives marketing approval, and we or others later identify undesirable side effects or adverse events caused by such products, a number of potentially significant negative consequences could result, including but not limited to:

- regulatory authorities may withdraw approvals of such product and cause us to recall our product;
- regulatory authorities may require additional warnings on the label;
- we may be required to change the way the product is administered or conduct additional clinical trials or post-approval studies;
- we may be required to create a Risk Evaluation and Mitigation Strategy plan, which could include a medication guide outlining the risks of such side effects for distribution to patients, a communication plan for healthcare providers, and/or other elements, such as boxed warning on the packaging, to assure safe use;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

[Table of Contents](#)

Any of these events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, and could significantly harm our business, results of operations, and prospects.

We may in the future conduct clinical trials for our product candidates outside the United States, and the FDA, EMA and applicable foreign regulatory authorities may not accept data from such trials.

We may in the future choose to conduct one or more of our clinical trials outside the United States, including in Europe. The acceptance of study data from clinical trials conducted outside the United States or another jurisdiction by the FDA, EMA or applicable foreign regulatory authority may be subject to certain conditions. In cases where data from foreign clinical trials are intended to serve as the basis for marketing approval in the United States, the FDA will generally not approve the application on the basis of foreign data alone unless (i) the data are applicable to the United States population and United States medical practice; and (ii) the trials were performed by clinical investigators of recognized competence and pursuant to cGCP regulations. Additionally, the FDA's clinical trial requirements, including sufficient size of patient populations and statistical powering, must be met. Many foreign regulatory bodies have similar approval requirements. In addition, such foreign trials would be subject to the applicable local laws of the foreign jurisdictions where the trials are conducted. There can be no assurance that the FDA, EMA or any applicable foreign regulatory authority will accept data from trials conducted outside of the United States or the applicable jurisdiction. If the FDA, EMA or any applicable foreign regulatory authority does not accept such data, it would result in the need for additional trials, which would be costly and time-consuming and delay aspects of our business plan, and which may result in our product candidates not receiving approval or clearance for commercialization in the applicable jurisdiction.

Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not mean that we will be successful in obtaining regulatory approval of our product candidates in other jurisdictions.

Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not guarantee that we will be able to obtain or maintain regulatory approval in any other jurisdiction, but a failure or delay in obtaining regulatory approval in one jurisdiction may have a negative effect on the regulatory approval process in others. For example, even if the FDA or EMA grants marketing approval of a product candidate, comparable regulatory authorities in foreign jurisdictions must also approve the manufacturing, marketing and promotion of the product candidate in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from those in the United States, including additional preclinical studies or clinical trials as clinical trials conducted in one jurisdiction may not be accepted by regulatory authorities in other jurisdictions. In many jurisdictions outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that jurisdiction. In some cases, the price that we intend to charge for our products is also subject to approval.

Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. If we or any partner we work with fail to comply with the regulatory requirements in international markets or fail to receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed.

Even if we obtain regulatory approval for a product candidate, our products will remain subject to extensive regulatory scrutiny.

[Table of Contents](#)

If any of our product candidates are approved, they will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping, conduct of post-marketing studies, and submission of safety, efficacy, and other post-market information, including both federal and state requirements in the United States and requirements of comparable foreign regulatory authorities.

Manufacturers and manufacturers' facilities are required to comply with extensive requirements imposed by the FDA, EMA and comparable foreign regulatory authorities, including ensuring that quality control and manufacturing procedures conform to cGMP regulations. As such, we and our contract manufacturers will be subject to continual review and inspections to assess compliance with cGMP and adherence to commitments made in any NDA, BLA or marketing authorization application, or MAA. Accordingly, we and others with whom we work must continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production and quality control.

Any regulatory approvals that we receive for our product candidates will be subject to limitations on the approved indicated uses for which the product may be marketed and promoted or to the conditions of approval (including the requirement to implement a Risk Evaluation and Mitigation Strategy), or contain requirements for potentially costly post-marketing testing. We will be required to report certain adverse reactions and production problems, if any, to the FDA, EMA and comparable foreign regulatory authorities. Any new legislation addressing drug safety issues could result in delays in product development or commercialization, or increased costs to assure compliance. The FDA and other agencies, including the Department of Justice, closely regulate and monitor the post-approval marketing and promotion of products to ensure that they are manufactured, marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. We will have to comply with requirements concerning advertising and promotion for our products. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved label. As such, we may not promote our products for indications or uses for which they do not have approval. The holder of an approved NDA, BLA, or MAA must submit new or supplemental applications and obtain approval for certain changes to the approved product, product labeling, or manufacturing process. We could also be asked to conduct post-marketing clinical trials to verify the safety and efficacy of our products in general or in specific patient subsets. If original marketing approval was obtained via the accelerated approval pathway, we could be required to conduct a successful post-marketing clinical trial to confirm clinical benefit for our products. An unsuccessful post-marketing study or failure to complete such a study could result in the withdrawal of marketing approval.

If a regulatory agency discovers previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, or disagrees with the promotion, marketing or labeling of a product, such regulatory agency may impose restrictions on that product or us, including requiring withdrawal of the product from the market. If we fail to comply with applicable regulatory requirements, a regulatory agency or enforcement authority may, among other things:

- issue warning letters that would result in adverse publicity;
- impose civil or criminal penalties;
- suspend or withdraw regulatory approvals;
- suspend any of our ongoing clinical trials;
- refuse to approve pending applications or supplements to approved applications submitted by us;
- impose restrictions on our operations, including closing our contract manufacturers' facilities;
- seize or detain products; or

[Table of Contents](#)

- require a product recall.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response, and could generate negative publicity. Any failure to comply with ongoing regulatory requirements may significantly and adversely affect our ability to commercialize and generate revenue from our products. If regulatory sanctions are applied or if regulatory approval is withdrawn, the value of our company and our operating results will be adversely affected.

We plan to seek orphan drug designation for some product candidates, but we may be unable to obtain such designations or to maintain the benefits associated with orphan drug status, including market exclusivity, which may cause our revenue, if any, to be reduced.

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biologic intended to treat a rare disease or condition, defined as a disease or condition with a patient population of fewer than 200,000 in the United States, or a patient population greater than 200,000 in the United States when there is no reasonable expectation that the cost of developing and making available the drug or biologic in the United States will be recovered from sales in the United States for that drug or biologic. Orphan drug designation must be requested before submitting an NDA or BLA. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages, and user-fee waivers. After the FDA grants orphan drug designation, the generic identity of the drug and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. We plan to seek orphan drug designations for some product candidates and may be unable to obtain such designations.

If a product that has orphan drug designation subsequently receives the first FDA approval for a particular active ingredient for the disease for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other NDA or BLA applications to market the same drug or biologic for the same indication for seven years, except in limited circumstances such as a showing of clinical superiority to the product with orphan exclusivity or if FDA finds that the holder of the orphan exclusivity has not shown that it can assure the availability of sufficient quantities of the orphan product to meet the needs of patients with the disease or condition for which the drug was designated. As a result, even if one of our product candidates receives orphan exclusivity, the FDA can still approve other drugs that have a different active ingredient for use in treating the same indication or disease. Furthermore, the FDA can waive orphan exclusivity if we are unable to manufacture sufficient supply of our product.

Healthcare legislative measures aimed at reducing healthcare costs may have a material adverse effect on our business and results of operations.

[Table of Contents](#)

Third-party payors, whether domestic or foreign, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In both the United States and certain foreign jurisdictions, there have been a number of legislative and regulatory changes to the health care system that could impact our ability to sell our products profitably. In particular, in 2010, the Affordable Care Act, or ACA, was enacted, which, among other things, subjected biologic products to potential competition by lower-cost biosimilars, addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program, extended the Medicaid Drug Rebate Program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations, subjected manufacturers to new annual fees and taxes for certain branded prescription drugs, and provided incentives to programs that increase the federal government's comparative effectiveness research. Recent changes in the U.S. administration could lead to repeal of or changes in some or all of the ACA, and complying with any new legislation or reversing changes implemented under the ACA could be time-intensive and expensive, resulting in a material adverse effect on our business. Until the ACA is fully implemented or there is more certainty concerning the future of the ACA, it will be difficult to predict its full impact and influence on our business.

In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in 2013, and will remain in effect through 2025 unless additional Congressional action is taken. The American Taxpayer Relief Act of 2012 further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at containing or lowering the cost of healthcare. We cannot predict the initiatives that may be adopted in the future. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare and/or impose price controls may adversely affect:

- the demand for our product candidates, if we obtain regulatory approval;
- our ability to receive or set a price that we believe is fair for our products;
- our ability to generate revenue and achieve or maintain profitability;
- the level of taxes that we are required to pay; and
- the availability of capital.

We expect that the ACA, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, lower reimbursement, and new payment methodologies. This could lower the price that we receive for any approved product. Any denial in coverage or reduction in reimbursement from Medicare or other government-funded programs may result in a similar denial or reduction in payments from private payors, which may prevent us from being able to generate sufficient revenue, attain profitability or commercialize our product candidates, if approved.

Our employees, independent contractors, consultants, commercial partners and vendors may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk of fraud, misconduct or other illegal activity by our employees, independent contractors, consultants, commercial partners and vendors. Misconduct by these parties could include intentional, reckless and negligent conduct that fails to: comply with the laws of the FDA, EMA and other comparable foreign regulatory authorities; provide true, complete and accurate information to the FDA, EMA and other comparable foreign regulatory authorities; comply with manufacturing standards we have established; comply with healthcare fraud and abuse laws in the United States and similar foreign fraudulent misconduct laws; or report financial information or data accurately or to disclose unauthorized activities to us. If we obtain FDA approval of any of our product candidates and begin commercializing those products in the United States, our potential exposure under such laws will increase significantly, and our costs associated with compliance with such laws are also likely to increase. In particular, research, sales, marketing, education and other business arrangements in the healthcare industry are subject to extensive laws designed to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, educating, marketing and promotion, sales and commission, certain customer incentive programs and other business arrangements generally. Activities subject to these laws also involve the improper use of information obtained in the course of patient recruitment for clinical trials, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of business conduct and ethics, but it is not always possible to identify and deter misconduct by employees and third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

If we fail to comply with healthcare laws, we could face substantial penalties and our business, operations and financial conditions could be adversely affected.

If we obtain FDA approval for any of our product candidates and begin commercializing those products in the United States, our operations will be subject to various federal and state fraud and abuse laws. The laws that may impact our operations include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe, or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act;
- federal civil and criminal false claims laws and civil monetary penalty laws, including the False Claims Act, which impose criminal and civil penalties, including through civil “qui tam” or “whistleblower” actions, against individuals or entities from knowingly presenting, or causing to be presented, claims for payment or approval from Medicare, Medicaid, or other third-party payors that are false or fraudulent or knowingly making a false statement to improperly avoid, decrease or conceal an obligation to pay money to the federal government. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of these statutes or specific intent to violate them in order to have committed a violation;

[Table of Contents](#)

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their respective implementing regulations, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information without appropriate authorization;
- the federal Physician Payment Sunshine Act, created under the ACA, and its implementing regulations, which require manufacturers of drugs, devices, biologicals and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program to report annually to the U.S. Department of Health and Human Services under the Open Payments Program, information related to payments or other transfers of value made to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members;
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers; and
- analogous state and foreign laws and regulations, such as state and foreign anti-kickback, false claims, consumer protection and unfair competition laws which may apply to pharmaceutical business practices, including but not limited to, research, distribution, sales and marketing arrangements as well as submitting claims involving healthcare items or services reimbursed by any third-party payer, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government that otherwise restricts payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to file reports with states regarding pricing and marketing information, such as the tracking and reporting of gifts, compensations and other remuneration and items of value provided to healthcare professionals and entities; and state and foreign laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

[Table of Contents](#)

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could, despite our efforts to comply, be subject to challenge under one or more of such laws. Efforts to ensure that our business arrangements will comply with applicable healthcare laws may involve substantial costs. It is possible that governmental and enforcement authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law interpreting applicable fraud and abuse or other healthcare laws and regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of civil, criminal and administrative penalties, damages, disgorgement, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations. In addition, the approval and commercialization of any of our product candidates outside the United States will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.

Our business is subject to complex and evolving U.S. and foreign laws and regulations relating to privacy and data protection. These laws and regulations are subject to change and uncertain interpretation, and could result in claims, changes to our business practices, or monetary penalties, and otherwise may harm our business.

A wide variety of provincial, state, national, and international laws and regulations apply to the collection, use, retention, protection, disclosure, transfer and other processing of personal data. These data protection and privacy-related laws and regulations are evolving and may result in ever-increasing regulatory and public scrutiny and escalating levels of enforcement and sanctions. For example, the European Union General Data Protection Regulation, or GDPR, which became fully effective on May 25, 2018, imposes stringent data protection requirements and provides for penalties for noncompliance of up to the greater of €20 million or four percent of worldwide annual revenues. The GDPR and many other laws and regulations relating to privacy and data protection are still being tested in courts, and they are subject to new and differing interpretations by courts and regulatory officials. We are working to comply with the GDPR and other privacy and data protection laws and regulations that apply to us, and we anticipate needing to devote significant additional resources to complying with these laws and regulations. It is possible that the GDPR or other laws and regulations relating to privacy and data protection may be interpreted and applied in a manner that is inconsistent from jurisdiction to jurisdiction or inconsistent with our current policies and practices.

Our actual or perceived failure to adequately comply with applicable laws and regulations relating to privacy and data protection, or to protect personal data and other data we process or maintain, could result in regulatory fines, investigations and enforcement actions, penalties and other liabilities, claims for damages by affected individuals, and damage to our reputation, any of which could materially affect our business, financial condition and results of operations.

If we or any contract manufacturers and suppliers we engage fail to comply with environmental, health, and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

[Table of Contents](#)

We and any contract manufacturers and suppliers we engage are subject to numerous federal, state, and local environmental, health, and safety laws, regulations, and permitting requirements, including those governing laboratory procedures; the generation, handling, use, storage, treatment, and disposal of hazardous and regulated materials and wastes; the emission and discharge of hazardous materials into the ground, air, and water; and employee health and safety. Our operations involve the use of hazardous and flammable materials, including chemicals and biological and radioactive materials. Our operations also produce hazardous waste. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. Under certain environmental laws, we could be held responsible for costs relating to any contamination at our current or past facilities and at third-party facilities. We also could incur significant costs associated with civil or criminal fines and penalties.

Compliance with applicable environmental laws and regulations may be expensive, and current or future environmental laws and regulations may impair our research, product development and manufacturing efforts. In addition, we cannot entirely eliminate the risk of accidental injury or contamination from these materials or wastes. Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not carry specific biological or hazardous waste insurance coverage, and our property, casualty, and general liability insurance policies specifically exclude coverage for damages and fines arising from biological or hazardous waste exposure or contamination. Accordingly, in the event of contamination or injury, we could be held liable for damages or be penalized with fines in an amount exceeding our resources, and our clinical trials or regulatory approvals could be suspended, which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

Our business activities may be subject to the Foreign Corrupt Practices Act, or FCPA, and similar anti-bribery and anti-corruption laws.

Our business activities may be subject to the FCPA and similar anti-bribery or anti-corruption laws, regulations or rules of other countries in which we operate, including the U.K. Bribery Act. The FCPA generally prohibits offering, promising, giving, or authorizing others to give anything of value, either directly or indirectly, to a non-U.S. government official in order to influence official action, or otherwise obtain or retain business. The FCPA also requires public companies to make and keep books and records that accurately and fairly reflect the transactions of the corporation and to devise and maintain an adequate system of internal accounting controls. Our business is heavily regulated and therefore involves significant interaction with public officials, including officials of non-U.S. governments. Additionally, in many other countries, the health care providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, our dealings with these prescribers and purchasers are subject to regulation under the FCPA. Recently the Securities and Exchange Commission, or SEC, and Department of Justice have increased their FCPA enforcement activities with respect to biotechnology and pharmaceutical companies. There is no certainty that all of our employees, agents, contractors, or collaborators, or those of our affiliates, will comply with all applicable laws and regulations, particularly given the high level of complexity of these laws. Violations of these laws and regulations could result in fines, criminal sanctions against us, our officers, or our employees, the closing down of our facilities, requirements to obtain export licenses, cessation of business activities in sanctioned countries, implementation of compliance programs, and prohibitions on the conduct of our business. Any such violations could include prohibitions on our ability to offer our products in one or more countries and could materially damage our reputation, our brand, our international expansion efforts, our ability to attract and retain employees, and our business, prospects, operating results, and financial condition.

Risks Related to Our Reliance on Third Parties

We expect to depend on collaborations with third parties for the research, development and commercialization of certain of the product candidates we may develop. If any such collaborations are not successful, we may not be able to realize the market potential of those product candidates.

We anticipate seeking third-party collaborators for the research, development, and commercialization of certain of the product candidates we may develop. For example, we have collaborations with F-star, Takeda and others, to further our development of product candidates and to enhance our research efforts directed to better understanding neurodegenerative diseases. Our likely collaborators for any other collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies, biotechnology companies and academic institutions. If we enter into any such arrangements with any third parties, we will likely have shared or limited control over the amount and timing of resources that our collaborators dedicate to the development or potential commercialization of any product candidates we may seek to develop with them. Our ability to generate revenue from these arrangements with commercial entities will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements. We cannot predict the success of any collaboration that we enter into.

Collaborations involving our research programs, or any product candidates we may develop, pose the following risks to us:

- collaborators generally have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not properly obtain, maintain, enforce, or defend intellectual property or proprietary rights relating to our product candidates or research programs or may use our proprietary information in such a way as to expose us to potential litigation or other intellectual property related proceedings, including proceedings challenging the scope, ownership, validity and enforceability of our intellectual property;
- collaborators may own or co-own intellectual property covering our product candidates or research programs that results from our collaboration with them, and in such cases, we may not have the exclusive right to commercialize such intellectual property or such product candidates or research programs;
- we may need the cooperation of our collaborators to enforce or defend any intellectual property we contribute to or that arises out of our collaborations, which may not be provided to us;
- collaborators may control certain interactions with regulatory authorities, which may impact on our ability to obtain and maintain regulatory approval of our products candidates;
- disputes may arise between the collaborators and us that result in the delay or termination of the research, development, or commercialization of our product candidates or research programs or that result in costly litigation or arbitration that diverts management attention and resources;
- collaborators may decide to not pursue development and commercialization of any product candidates we develop or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborator's strategic focus or available funding or external factors such as an acquisition that diverts resources or creates competing priorities;

[Table of Contents](#)

- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials, or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates or research programs if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- collaborators may restrict us from researching, developing or commercializing certain products or technologies without their involvement;
- collaborators with marketing and distribution rights to one or more product candidates may not commit sufficient resources to the marketing and distribution of such product candidates;
- we may lose certain valuable rights under circumstances identified in our collaborations, including if we undergo a change of control;
- collaborators may grant sublicenses to our technology or product candidates or undergo a change of control and the sublicensees or new owners may decide to take the collaboration in a direction which is not in our best interest;
- collaborators may become bankrupt, which may significantly delay our research or development programs, or may cause us to lose access to valuable technology, know-how or intellectual property of the collaborator relating to our products, product candidates or research programs;
- key personnel at our collaborators may leave, which could negatively impact our ability to productively work with our collaborators;
- collaborations may require us to incur short and long-term expenditures, issue securities that dilute our stockholders, or disrupt our management and business;
- If our collaborators do not satisfy their obligations under our agreements with them, or if they terminate our collaborations with them, we may not be able to develop or commercialize product candidates as planned;
- collaborations may require us to share in development and commercialization costs pursuant to budgets that we do not fully control and our failure to share in such costs could have a detrimental impact on the collaboration or our ability to share in revenue generated under the collaboration;
- collaborations may be terminated in their entirety or with respect to certain product candidates or technologies and, if so terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates or technologies, including our BBB platform technology; and
- collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If a present or future collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our development or commercialization program under such collaboration could be delayed, diminished, or terminated.

[Table of Contents](#)

We may face significant competition in seeking appropriate collaborations. Recent business combinations among biotechnology and pharmaceutical companies have resulted in a reduced number of potential collaborators. In addition, the negotiation process is time-consuming and complex, and we may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of the product candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop product candidates or bring them to market and generate product revenue.

If we enter into collaborations to develop and potentially commercialize any product candidates, we may not be able to realize the benefit of such transactions if we or our collaborator elects not to exercise the rights granted under the agreement or if we or our collaborator are unable to successfully integrate a product candidate into existing operations and company culture. In addition, if our agreement with any of our collaborators terminates, our access to technology and intellectual property licensed to us by that collaborator may be restricted or terminate entirely, which may delay our continued development of our product candidates utilizing the collaborator's technology or intellectual property or require us to stop development of those product candidates completely. We may also find it more difficult to find a suitable replacement collaborator or attract new collaborators, and our development programs may be delayed or the perception of us in the business and financial communities could be adversely affected. Many of the risks relating to product development, regulatory approval, and commercialization described in this "Risk Factors" section also apply to the activities of our collaborators and any negative impact on our collaborators may adversely affect us.

We expect to rely on third parties to conduct our clinical trials and some aspects of our research and preclinical testing, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials, research, or testing.

We currently rely and expect to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions, and clinical investigators, to conduct some aspects of our research and preclinical testing and our clinical trials. Any of these third parties may terminate their engagements with us or be unable to fulfill their contractual obligations. If we need to enter into alternative arrangements, it would delay our product development activities.

Our reliance on these third parties for research and development activities reduces our control over these activities but does not relieve us of our responsibilities. For example, we remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with cGCPs for conducting, recording, and reporting the results of clinical trials to assure that data and reported results are credible, reproducible and accurate and that the rights, integrity, and confidentiality of trial participants are protected. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database within certain timeframes. Failure to do so can result in fines, adverse publicity, and civil and criminal sanctions.

If these third parties do not successfully carry out their contractual duties, meet expected deadlines, or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for any product candidates we may develop and will not be able to, or may be delayed in our efforts to, successfully commercialize our medicines.

[Table of Contents](#)

We also expect to rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors, including with the shipment of any drug supplies, could delay clinical development or marketing approval of any product candidates we may develop or commercialization of our medicines, producing additional losses and depriving us of potential product revenue.

We contract with third parties for the manufacture of materials for our research programs and preclinical studies and expect to continue to do so for clinical trials and for commercialization of any product candidates that we may develop. This reliance on third parties carries and may increase the risk that we will not have sufficient quantities of such materials, product candidates, or any medicines that we may develop and commercialize, or that such supply will not be available to us at an acceptable cost, which could delay, prevent, or impair our development or commercialization efforts.

We do not have any manufacturing facilities. We currently rely on third-party manufacturers for the manufacture of our materials for preclinical studies and clinical trials and expect to continue to do so for preclinical studies, clinical trials and for commercial supply of any product candidates that we may develop.

We may be unable to establish any further agreements with third-party manufacturers or to do so on acceptable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- the possible breach of the manufacturing agreement by the third party;
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us;
- reliance on the third party for regulatory compliance, quality assurance, safety, and pharmacovigilance and related reporting; and
- the inability to produce required volume in a timely manner and to quality standards.

Third-party manufacturers may not be able to comply with cGMP regulations or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in clinical holds on our trials, sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocations, seizures or recalls of product candidates or medicines, operating restrictions, and criminal prosecutions, any of which could significantly and adversely affect supplies of our medicines and harm our business, financial condition, results of operations, and prospects.

Any medicines that we may develop may compete with other product candidates and products for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply for any of our product candidates. If any one of our current contract manufacturers cannot perform as agreed, we may be required to replace that manufacturer and may incur added costs and delays in identifying and qualifying any such replacement. Furthermore, securing and reserving production capacity with contract manufacturers may result in significant costs.

Our current and anticipated future dependence upon others for the manufacture of any product candidates we may develop or medicines may adversely affect our future profit margins and our ability to commercialize any medicines that receive marketing approval on a timely and competitive basis.

We depend on third-party suppliers for key raw materials used in our manufacturing processes, and the loss of these third-party suppliers or their inability to supply us with adequate raw materials could harm our business.

We rely on third-party suppliers for the raw materials required for the production of our product candidates. Our dependence on these third-party suppliers and the challenges we may face in obtaining adequate supplies of raw materials involve several risks, including limited control over pricing, availability, quality and delivery schedules. As a small company, our negotiation leverage is limited and we are likely to get lower priority than our competitors who are larger than we are. We cannot be certain that our suppliers will continue to provide us with the quantities of these raw materials that we require or satisfy our anticipated specifications and quality requirements. Any supply interruption in limited or sole sourced raw materials could materially harm our ability to manufacture our product candidates until a new source of supply, if any, could be identified and qualified. We may be unable to find a sufficient alternative supply channel in a reasonable time or on commercially reasonable terms. Any performance failure on the part of our suppliers could delay the development and potential commercialization of our product candidates, including limiting supplies necessary for clinical trials and regulatory approvals, which would have a material adverse effect on our business.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain patent protection for any product candidates we develop or for our BBB platform technology, our competitors could develop and commercialize products or technology similar or identical to ours, and our ability to successfully commercialize any product candidates we may develop, and our technology may be adversely affected.

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our BBB platform technology and any proprietary product candidates and other technologies we may develop. We seek to protect our proprietary position by in-licensing intellectual property and filing patent applications in the United States and abroad relating to our BBB platform technology, core programs and product candidates, as well as other technologies that are important to our business. Given that the development of our technology and product candidates is at an early stage, our intellectual property portfolio with respect to certain aspects of our technology and product candidates is also at an early stage. For example, as of September 30, 2018, we do not own or in-license any issued patents in the United States directed to the composition of matter of any of the antibodies or enzymes that we have thus far developed using our BBB platform technology. In addition, we do not own or in-license any issued United States patents covering the composition of matter of the Fc domain portion of our BBB platform technology that binds to transferrin receptor, or any issued United States patents that cover the composition of matter of antibodies or enzymes being developed in our TREM2, aSyn, or IDS core programs. We have filed or intend to file patent applications on these aspects of our technology and core product candidates; however, there can be no assurance that any such patent applications will issue as granted patents. Furthermore, in some cases, we have only filed provisional patent applications on certain aspects of our technology and product candidates and each of these provisional patent applications is not eligible to become an issued patent until, among other things, we file a non-provisional patent application within 12 months of the filing date of the applicable provisional patent application. Any failure to file a non-provisional patent application within this timeline could cause us to lose the ability to obtain patent protection for the inventions disclosed in the associated provisional patent applications. Furthermore, in some cases, we may not be able to obtain issued claims covering compositions relating to our BBB platform technology, core programs and product candidates, as well as other technologies that are important to our business, and instead may need to rely on filing patent applications with claims covering a method of use and/or method of manufacture for protection of such BBB platform technology, core programs, product candidates and other technologies. There can be no assurance that any such patent applications will issue as granted patents, and even if they do issue, such patent claims may be insufficient to prevent third parties, such as our competitors, from utilizing our technology. Any failure to obtain or maintain patent protection with respect to our BBB platform technology, core programs and product candidates could have a material adverse effect on our business, financial condition, results of operations, and prospects.

If any of our owned or in-licensed patent applications do not issue as patents in any jurisdiction, we may not be able to compete effectively.

Changes in either the patent laws or their interpretation in the United States and other countries may diminish our ability to protect our inventions, obtain, maintain, and enforce our intellectual property rights and, more generally, could affect the value of our intellectual property or narrow the scope of our owned and licensed patents. With respect to both in-licensed and owned intellectual property, we cannot predict whether the patent applications we and our licensors are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient protection from competitors or other third parties.

The patent prosecution process is expensive, time-consuming, and complex, and we may not be able to file, prosecute, maintain, enforce, or license all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output in time to obtain patent protection. Although we enter into non-disclosure and confidentiality agreements with parties who have access to confidential or patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, CROs, contract manufacturers, consultants, advisors, and other third parties, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. In addition, our ability to obtain and maintain valid and enforceable patents depends on whether the differences between our inventions and the prior art allow our inventions to be patentable over the prior art. Furthermore, publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we or our licensors were the first to make the inventions claimed in any of our owned or licensed patents or pending patent applications, or that we or our licensors were the first to file for patent protection of such inventions.

If the scope of any patent protection we obtain is not sufficiently broad, or if we lose any of our patent protection, our ability to prevent our competitors from commercializing similar or identical technology and product candidates would be adversely affected.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions, and has been the subject of much litigation in recent years. As a result, the issuance, scope, validity, enforceability, and commercial value of our patent rights are highly uncertain. Our owned or in-licensed pending and future patent applications may not result in patents being issued which protect our BBB platform technology, product candidates or other technologies or which effectively prevent others from commercializing competitive technologies and product candidates.

Moreover, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Even if patent applications we license or own currently or in the future issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us, or otherwise provide us with any competitive advantage. Any patents that we own or in-license may be challenged, narrowed, circumvented, or invalidated by third parties. Consequently, we do not know whether our BBB platform technology, product candidates or other technologies will be protectable or remain protected by valid and enforceable patents. Our competitors or other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner which could materially adversely affect our business, financial condition, results of operations and prospects.

[Table of Contents](#)

The issuance of a patent is not conclusive as to its inventorship, scope, validity, or enforceability, and our patents may be challenged in the courts or patent offices in the United States and abroad. We or our licensors may be subject to a third-party preissuance submission of prior art to the United States Patent and Trademark Office, or USPTO, or become involved in opposition, derivation, revocation, reexamination, post-grant and *inter partes* review, or interference proceedings or other similar proceedings challenging our owned or licensed patent rights. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate or render unenforceable, our owned or in-licensed patent rights, allow third parties to commercialize our BBB platform technology, product candidates or other technologies and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. Moreover, we, or one of our licensors, may have to participate in interference proceedings declared by the USPTO to determine priority of invention or in post-grant challenge proceedings, such as oppositions in a foreign patent office, that challenge our or our licensor's priority of invention or other features of patentability with respect to our owned or in-licensed patents and patent applications. Such challenges may result in loss of patent rights, loss of exclusivity, or in patent claims being narrowed, invalidated, or held unenforceable, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our BBB platform technology, product candidates and other technologies. Such proceedings also may result in substantial cost and require significant time from our scientists and management, even if the eventual outcome is favorable to us.

In addition, given the amount of time required for the development, testing, and regulatory review of new product candidates, patents protecting such product candidates might expire before or shortly after such product candidates are commercialized. As a result, our intellectual property may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. Some of our owned and in-licensed patents and patent applications are, and may in the future be, co-owned with third parties. For example, we currently, and may in the future, co-own certain patents and patent applications relating to our BBB platform technology with F-star. In addition, certain of our licensors co-own the patents and patent applications we in-license with other third parties with whom we do not have a direct relationship. Our exclusive rights to certain of these patents and patent applications are dependent, in part, on inter-institutional or other operating agreements between the joint owners of such patents and patent applications, who are not parties to our license agreements. For example, under our license agreement with VIB, we license certain patents and patent applications co-owned by VIB and KU Leuven. Our rights to KU Leuven's interest in such patents and patent applications depends on an operating agreement between VIB and KU Leuven, pursuant to which VIB controls the licensing of such patents and patent applications. If our licensors do not have exclusive control of the grant of licenses under any such third-party co-owners' interest in such patents or patent applications or we are otherwise unable to secure such exclusive rights, such co-owners may be able to license their rights to other third parties, including our competitors, and our competitors could market competing products and technology. In addition, we may need the cooperation of any such co-owners of our patents in order to enforce such patents against third parties, and such cooperation may not be provided to us. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

Our rights to develop and commercialize our BBB platform technology and product candidates are subject, in part, to the terms and conditions of licenses granted to us by others.

We are heavily reliant upon licenses to certain patent rights and proprietary technology from third parties that are important or necessary to the development of our BBB platform technology and product candidates. For example, in June 2016, we entered into a license agreement with Genentech pursuant to which we received an exclusive license to certain of Genentech's intellectual property relating to our LRRK2 program, including our DNL201 and DNL151 product candidates. In March 2017, we entered into an exclusive license agreement with VIB pursuant to which we received exclusive and non-exclusive licenses to certain patent rights and related know-how pertaining to antibodies that target BACE1.

[Table of Contents](#)

In addition, our agreements with F-star and other license agreements may not provide exclusive rights to use certain licensed intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology and products in the future. For example, F-star retains the right to use itself, and to license to others, its modular antibody technology for any purpose other than the targets and antibodies which we have agreed with F-star would or may be exclusively available to us. As a result, we may not be able to prevent competitors or other third parties from developing and commercializing competitive products that also utilizes technology that we have in-licensed.

In addition, subject to the terms of any such license agreements, we do not have the right to control the preparation, filing, prosecution and maintenance, and we may not have the right to control the enforcement, and defense of patents and patent applications covering the technology that we license from third parties. For example, under our agreements with F-star and Genentech, the licensors control prosecution and, in the case of F-star and in specified circumstances, enforcement of certain of the patents and patent applications licensed to us. We cannot be certain that our in-licensed patents and patent applications that are controlled by our licensors will be prepared, filed, prosecuted, maintained, enforced, and defended in a manner consistent with the best interests of our business. If our licensors fail to prosecute, maintain, enforce, and defend such patents, or lose rights to those patents or patent applications, the rights we have licensed may be reduced or eliminated, our right to develop and commercialize our BBB platform technology and any of our product candidates that are subject of such licensed rights could be adversely affected, and we may not be able to prevent competitors from making, using and selling competing products. In addition, even where we have the right to control patent prosecution of patents and patent applications we have licensed to and from third parties, we may still be adversely affected or prejudiced by actions or inactions of our licensees, our licensors and their counsel that took place prior to the date upon which we assumed control over patent prosecution.

Furthermore, our owned and in-licensed patents may be subject to a reservation of rights by one or more third parties. For example, our license to certain intellectual property owned by Genentech is subject to certain research rights Genentech granted to third parties prior to our license agreement. In addition, certain of our in-licensed intellectual property relating to RIPK1 was funded in part by the U.S. government. As a result, the U.S. government may have certain rights to such intellectual property. When new technologies are developed with U.S. government funding, the U.S. government generally obtains certain rights in any resulting patents, including a non-exclusive license authorizing the U.S. government to use the invention or to have others use the invention on its behalf. The U.S. government's rights may also permit it to disclose the funded inventions and technology to third parties and to exercise march-in rights to use or allow third parties to use the technology we have licensed that was developed using U.S. government funding. The U.S. government may exercise its march-in rights if it determines that action is necessary because we fail to achieve practical application of the government-funded technology, or because action is necessary to alleviate health or safety needs, to meet requirements of federal regulations, or to give preference to U.S. industry. In addition, our rights in such inventions may be subject to certain requirements to manufacture products embodying such inventions in the United States in certain circumstances and if this requirement is not waived. Any exercise by the U.S. government of such rights or by any third party of its reserved rights could have a material adverse effect on our competitive position, business, financial condition, results of operations, and prospects.

If we fail to comply with our obligations in the agreements under which we license intellectual property rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.

[Table of Contents](#)

We have entered into license agreements with third parties and may need to obtain additional licenses from others to advance our research or allow commercialization of product candidates we may develop or our BBB platform technology. It is possible that we may be unable to obtain additional licenses at a reasonable cost or on reasonable terms, if at all. In that event, we may be required to expend significant time and resources to redesign our technology, product candidates, or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize the affected product candidates or continue to utilize our existing BBB platform technology, which could harm our business, financial condition, results of operations, and prospects significantly. We cannot provide any assurances that third-party patents do not exist which might be enforced against our current technology, including our BBB platform technology, manufacturing methods, product candidates, or future methods or products resulting in either an injunction prohibiting our manufacture or future sales, or, with respect to our future sales, an obligation on our part to pay royalties and/or other forms of compensation to third parties, which could be significant.

In addition, each of our license agreements, and we expect our future agreements, will impose various development, diligence, commercialization, and other obligations on us. Certain of our license agreements also require us to meet development timelines, or to exercise commercially reasonable efforts to develop and commercialize licensed products, in order to maintain the licenses. In spite of our efforts, our licensors might conclude that we have materially breached our obligations under such license agreements and might therefore terminate the license agreements, thereby removing or limiting our ability to develop and commercialize products and technology covered by these license agreements. If these in-licenses are terminated, or if the underlying patents fail to provide the intended exclusivity, competitors or other third parties would have the freedom to seek regulatory approval of, and to market, products identical to ours and we may be required to cease our development and commercialization of certain of our product candidates or of our current BBB platform technology. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

Moreover, disputes may arise regarding intellectual property subject to a licensing agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights under our collaborative development relationships;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the inventorship and ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- the priority of invention of patented technology.

[Table of Contents](#)

In addition, the agreements under which we currently license intellectual property or technology from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could have a material adverse effect on our business, financial condition, results of operations, and prospects. Moreover, if disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on commercially acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates, which could have a material adverse effect on our business, financial conditions, results of operations, and prospects.

We may not be able to protect our intellectual property and proprietary rights throughout the world.

Filing, prosecuting, and defending patents on our BBB platform technology, product candidates and other technologies in all countries throughout the world would be prohibitively expensive, and the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection but enforcement is not as strong as that in the United States. These products may compete with our products, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets, and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our intellectual property and proprietary rights generally. Proceedings to enforce our intellectual property and proprietary rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly, could put our patent applications at risk of not issuing, and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property and proprietary rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license. Many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we or any of our licensors is forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired, and our business, financial condition, results of operations, and prospects may be adversely affected.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment, and other requirements imposed by government patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

[Table of Contents](#)

Periodic maintenance fees, renewal fees, annuity fees, and various other government fees on patents and applications will be due to be paid to the USPTO and various government patent agencies outside of the United States over the lifetime of our owned or licensed patents and applications. In certain circumstances, we rely on our licensing partners to pay these fees due to U.S. and non-U.S. patent agencies. The USPTO and various non-U.S. government agencies require compliance with several procedural, documentary, fee payment, and other similar provisions during the patent application process. We are also dependent on our licensors to take the necessary action to comply with these requirements with respect to our licensed intellectual property. In some cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. There are situations, however, in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in a partial or complete loss of patent rights in the relevant jurisdiction. In such an event, potential competitors might be able to enter the market with similar or identical products or technology, which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.

Changes in either the patent laws or interpretation of the patent laws in the United States could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. Assuming that other requirements for patentability are met, prior to March 2013, in the United States, the first to invent the claimed invention was entitled to the patent, while outside the United States, the first to file a patent application was entitled to the patent. After March 2013, under the Leahy-Smith America Invents Act, or the America Invents Act, enacted in September 2011, the United States transitioned to a first inventor to file system in which, assuming that other requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third party was the first to invent the claimed invention. A third party that files a patent application in the USPTO after March 2013, but before us could therefore be awarded a patent covering an invention of ours even if we had made the invention before it was made by such third party. This will require us to be cognizant going forward of the time from invention to filing of a patent application. Since patent applications in the United States and most other countries are confidential for a period of time after filing or until issuance, we cannot be certain that we or our licensors were the first to either (i) file any patent application related to our BBB platform technology, product candidates or other technologies or (ii) invent any of the inventions claimed in our or our licensor's patents or patent applications.

The America Invents Act also includes a number of significant changes that affect the way patent applications will be prosecuted and also may affect patent litigation. These include allowing third-party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent by USPTO administered post-grant proceedings, including post-grant review, *inter partes* review, and derivation proceedings. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in United States federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action. Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action. Therefore, the America Invents Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our owned or in-licensed patent applications and the enforcement or defense of our owned or in-licensed issued patents, all of which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

[Table of Contents](#)

In addition, the patent positions of companies in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. This combination of events has created uncertainty with respect to the validity and enforceability of patents, once obtained. Depending on future actions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could have a material adverse effect on our existing patent portfolio and our ability to protect and enforce our intellectual property in the future.

Issued patents covering our BBB platform technology, product candidates and other technologies could be found invalid or unenforceable if challenged in court or before administrative bodies in the United States or abroad.

If we or one of our licensors initiated legal proceedings against a third party to enforce a patent covering our BBB platform technology, product candidates or other technologies, the defendant could counterclaim that such patent is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. Third parties may raise claims challenging the validity or enforceability of our owned or in-licensed patents before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post-grant review, *inter partes* review, interference proceedings, derivation proceedings, and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). Such proceedings could result in the revocation of, cancellation of, or amendment to our patents in such a way that they no longer cover our BBB platform technology, product candidates or other technologies. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we or our licensing partners and the patent examiner were unaware during prosecution. If a third party were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our BBB platform technology, product candidates or other technologies. Such a loss of patent protection would have a material adverse impact on our business, financial condition, results of operations, and prospects.

If we do not obtain patent term extension and data exclusivity for any product candidates we may develop, our business may be materially harmed.

Depending upon the timing, duration and specifics of any FDA marketing approval of any product candidates we may develop, one or more of our owned or in-licensed U.S. patents may be eligible for limited patent term extension under the Hatch-Waxman Act. The Hatch-Waxman Act permit a patent term extension of up to five years as compensation for patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent may be extended and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended. Similar extensions as compensation for patent term lost during regulatory review processes are also available in certain foreign countries and territories, such as in Europe under a Supplementary Patent Certificate. However, we may not be granted an extension in the United States and/or foreign countries and territories because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents, or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or the term of any such extension is shorter than what we request, our competitors may obtain approval of competing products following our patent expiration, and our business, financial condition, results of operations and prospects could be materially harmed.

We may be subject to claims challenging the inventorship of our patents and other intellectual property.

We or our licensors may be subject to claims that former employees, collaborators or other third parties have an interest in our owned or in-licensed patents, trade secrets, or other intellectual property as an inventor or co-inventor. For example, we or our licensors may have inventorship disputes arise from conflicting obligations of employees, consultants or others who are involved in developing our BBB platform technology, product candidates or other technologies. Litigation may be necessary to defend against these and other claims challenging inventorship or our or our licensors' ownership of our owned or in-licensed patents, trade secrets or other intellectual property. If we or our licensors fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, intellectual property that is important to our BBB platform technology, product candidates and other technologies. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to seeking patents for our BBB platform technology, product candidates and other technologies, we also rely on trade secrets and confidentiality agreements to protect our unpatented know-how, technology, and other proprietary information and to maintain our competitive position. Trade secrets and know-how can be difficult to protect. We expect our trade secrets and know-how to over time be disseminated within the industry through independent development, the publication of journal articles describing the methodology, and the movement of personnel from academic to industry scientific positions.

We seek to protect these trade secrets and other proprietary technology, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, CROs, contract manufacturers, consultants, advisors, and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants as well as train our employees not to bring or use proprietary information or technology from former employers to us or in their work, and remind former employees when they leave their employment of their confidentiality obligations. We cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology and processes. Despite our efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive, and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third party, our competitive position would be materially and adversely harmed.

We may not be successful in obtaining, through acquisitions, in-licenses or otherwise, necessary rights to our BBB platform technology, product candidates or other technologies.

[Table of Contents](#)

We currently have rights to intellectual property, through licenses from third parties, to identify and develop our BBB platform technology and product candidates. Many pharmaceutical companies, biotechnology companies, and academic institutions are competing with us in the field of neurodegeneration and BBB technology and may have patents and have filed and are likely filing patent applications potentially relevant to our business. In order to avoid infringing these third-party patents, we may find it necessary or prudent to obtain licenses to such patents from such third party intellectual property holders. We may also require licenses from third parties for certain BBB technologies that we are evaluating for use with our current or future product candidates. In addition, with respect to any patents we co-own with third parties, we may require licenses to such co-owners' interest to such patents. However, we may be unable to secure such licenses or otherwise acquire or in-license any compositions, methods of use, processes, or other intellectual property rights from third parties that we identify as necessary for our current or future product candidates and our BBB platform technology. The licensing or acquisition of third-party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third-party intellectual property rights that we may consider attractive or necessary. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment or at all. If we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of the relevant program or product candidate, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

We may be subject to claims that our employees, consultants, or advisors have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting ownership of what we regard as our own intellectual property.

Many of our employees, consultants, and advisors are currently or were previously employed at universities or other biotechnology or pharmaceutical companies, including our licensors, competitors and potential competitors. Although we try to ensure that our employees, consultants, and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that we or these individuals have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

In addition, while it is our policy to require our employees and contractors who may be involved in the conception or development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own. The assignment of intellectual property rights may not be self-executing, or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property. Such claims could have a material adverse effect on our business, financial condition, results of operations, and prospects.

Third-party claims of intellectual property infringement, misappropriation or other violation against us, our licensors or our collaborators may prevent or delay the development and commercialization of our BBB platform technology, product candidates and other technologies.

[Table of Contents](#)

The field of discovering treatments for neurodegenerative diseases, especially using BBB technology, is highly competitive and dynamic. Due to the focused research and development that is taking place by several companies, including us and our competitors, in this field, the intellectual property landscape is in flux, and it may remain uncertain in the future. As such, there may be significant intellectual property related litigation and proceedings relating to our owned and in-licensed, and other third party, intellectual property and proprietary rights in the future.

Our commercial success depends in part on our, our licensors' and our collaborators' ability to avoid infringing, misappropriating and otherwise violating the patents and other intellectual property rights of third parties. There is a substantial amount of complex litigation involving patents and other intellectual property rights in the biotechnology and pharmaceutical industries, as well as administrative proceedings for challenging patents, including interference, derivation and reexamination proceedings before the USPTO or oppositions and other comparable proceedings in foreign jurisdictions. As discussed above, recently, due to changes in U.S. law referred to as patent reform, new procedures including inter partes review and post-grant review have been implemented. As stated above, this reform adds uncertainty to the possibility of challenge to our patents in the future.

Numerous U.S. and foreign issued patents and pending patent applications owned by third parties exist relating to BBB technology and in the fields in which we are developing our product candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our BBB platform technology, product candidates and other technologies may give rise to claims of infringement of the patent rights of others. We cannot assure you that our BBB platform technology, product candidates and other technologies that we have developed, are developing or may develop in the future will not infringe existing or future patents owned by third parties. We may not be aware of patents that have already been issued and that a third party, for example, a competitor in the fields in which we are developing our BBB platform technology, product candidates, and other technologies might assert are infringed by our current or future BBB platform technology, product candidates or other technologies, including claims to compositions, formulations, methods of manufacture or methods of use or treatment that cover our BBB platform technology, product candidates or other technologies. It is also possible that patents owned by third parties of which we are aware, but which we do not believe are relevant to our BBB platform technology, product candidates or other technologies, could be found to be infringed by our BBB platform technology, product candidates or other technologies. In addition, because patent applications can take many years to issue, there may be currently pending patent applications that may later result in issued patents that our BBB platform technology, product candidates or other technologies may infringe.

Third parties may have patents or obtain patents in the future and claim that the manufacture, use or sale of our BBB platform technology, product candidates or other technologies infringes upon these patents. In the event that any third-party claims that we infringe their patents or that we are otherwise employing their proprietary technology without authorization and initiates litigation against us, even if we believe such claims are without merit, a court of competent jurisdiction could hold that such patents are valid, enforceable and infringed by our BBB platform technology, product candidates or other technologies. In this case, the holders of such patents may be able to block our ability to commercialize the applicable product candidate or technology unless we obtain a license under the applicable patents, or until such patents expire or are finally determined to be held invalid or unenforceable. Such a license may not be available on commercially reasonable terms or at all. Even if we are able to obtain a license, the license would likely obligate us to pay license fees or royalties or both, and the rights granted to us might be nonexclusive, which could result in our competitors gaining access to the same intellectual property. If we are unable to obtain a necessary license to a third-party patent on commercially reasonable terms, we may be unable to commercialize our BBB platform technology, product candidates or other technologies, or such commercialization efforts may be significantly delayed, which could in turn significantly harm our business.

[Table of Contents](#)

Defense of infringement claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of management and other employee resources from our business, and may impact our reputation. In the event of a successful claim of infringement against us, we may be enjoined from further developing or commercializing our infringing BBB platform technology, product candidates or other technologies. In addition, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties and/or redesign our infringing product candidates or technologies, which may be impossible or require substantial time and monetary expenditure. In that event, we would be unable to further develop and commercialize our BBB platform technology, product candidates or other technologies, which could harm our business significantly.

Engaging in litigation to defend against third parties alleging that we have infringed, misappropriated or otherwise violated their patents or other intellectual property rights is very expensive, particularly for a company of our size, and time-consuming. Some of our competitors may be able to sustain the costs of litigation or administrative proceedings more effectively than we can because of greater financial resources. Patent litigation and other proceedings may also absorb significant management time. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings against us could impair our ability to compete in the marketplace. The occurrence of any of the foregoing could have a material adverse effect on our business, financial condition or results of operations.

We may become involved in lawsuits to protect or enforce our patents and other intellectual property rights, which could be expensive, time consuming, and unsuccessful.

Competitors may infringe our patents or the patents of our licensing partners, or we may be required to defend against claims of infringement. In addition, our patents or the patents of our licensing partners also may become involved in inventorship, priority or validity disputes. To counter or defend against such claims can be expensive and time consuming. In an infringement proceeding, a court may decide that a patent owned or in-licensed by us is invalid or unenforceable, the other party's use of our patented technology falls under the safe harbor to patent infringement under 35 U.S.C. §271(e)(1), or may refuse to stop the other party from using the technology at issue on the grounds that our owned and in-licensed patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our owned or in-licensed patents at risk of being invalidated or interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions, or other interim proceedings or developments, and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing, or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected.

[Table of Contents](#)

Our registered or unregistered trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors or other third parties may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks or trade names. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely affect our business, financial condition, results of operations and prospects.

Intellectual property rights do not necessarily address all potential threats.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations and may not adequately protect our business or permit us to maintain our competitive advantage. For example:

- others may be able to make products that are similar to our product candidates or utilize similar technology but that are not covered by the claims of the patents that we license or may own;
- we, or our current or future licensors or collaborators, might not have been the first to make the inventions covered by the issued patent or pending patent application that we license or own now or in the future;
- we, or our current or future licensors or collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our owned or licensed intellectual property rights;
- it is possible that our current or future pending owned or licensed patent applications will not lead to issued patents;
- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors or other third parties;
- our competitors or other third parties might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents of others may harm our business; and
- we may choose not to file a patent in order to maintain certain trade secrets or know-how, and a third party may subsequently file a patent covering such intellectual property.

Should any of these events occur, they could have a material adverse effect on our business, financial condition, results of operations and prospects.

Risks Related to Our Operations

We are highly dependent on our key personnel, and if we are not successful in attracting, motivating and retaining highly qualified personnel, we may not be able to successfully implement our business strategy.

Our ability to compete in the highly competitive biotechnology and pharmaceutical industries depends upon our ability to attract, motivate and retain highly qualified managerial, scientific and medical personnel. We are highly dependent on our management, particularly our Chief Executive Officer, Dr. Ryan Watts, and our scientific and medical personnel. The loss of the services provided by any of our executive officers, other key employees, and other scientific and medical advisors, and our inability to find suitable replacements, could result in delays in the development of our product candidates and harm our business.

We conduct our operations at our facility in South San Francisco, California, in a region that is headquarters to many other biopharmaceutical companies and many academic and research institutions. Competition for skilled personnel is intense and the turnover rate can be high, which may limit our ability to hire and retain highly qualified personnel on acceptable terms or at all. We expect that we may need to recruit talent from outside of our region, and doing so may be costly and difficult.

To induce valuable employees to remain at our company, in addition to salary and cash incentives, we have provided restricted stock and stock option grants that vest over time. The value to employees of these equity grants that vest over time may be significantly affected by movements in our stock price that are beyond our control, and may at any time be insufficient to counteract more lucrative offers from other companies. Although we have employment agreements with our key employees, these employment agreements provide for at-will employment, which means that any of our employees could leave our employment at any time, with or without notice. We do not maintain "key man" insurance policies on the lives of all of these individuals or the lives of any of our other employees. If we are unable to attract and incentivize quality personnel on acceptable terms, or at all, it may cause our business and operating results to suffer.

We will need to grow the size and capabilities of our organization, and we may experience difficulties in managing this growth.

As of September 30, 2018, we had approximately 170 employees, all of whom were full-time. As our development plans and strategies develop, and as we transition into operating as a public company, we must add a significant number of additional managerial, operational, financial, and other personnel. Future growth will impose significant added responsibilities on members of management, including:

- identifying, recruiting, integrating, retaining, and motivating additional employees;
- managing our internal development efforts effectively, including the clinical and FDA review process for our current and future product candidates, while complying with our contractual obligations to contractors and other third parties;
- expanding our operational, financial and management controls, reporting systems, and procedures; and
- managing increasing operational and managerial complexity.

[Table of Contents](#)

Our future financial performance and our ability to continue to develop and, if approved, commercialize our product candidates will depend, in part, on our ability to effectively manage any future growth. Our management may also have to divert a disproportionate amount of its attention away from day-to-day activities in order to manage these growth activities. Our ability to successfully manage our expected growth is uncertain given the fact that all of our executive officers have joined us since February 2015. This lack of long-term experience working together as a company may adversely impact our senior management team's ability to effectively manage our business and growth.

We currently rely, and for the foreseeable future will continue to rely, in substantial part on certain independent organizations, advisors and consultants to provide certain services. There can be no assurance that the services of these independent organizations, advisors and consultants will continue to be available to us on a timely basis when needed, or that we can find qualified replacements. In addition, if we are unable to effectively manage our outsourced activities or if the quality or accuracy of the services provided by consultants is compromised for any reason, our clinical trials may be extended, delayed, or terminated, and we may not be able to obtain regulatory approval of our product candidates or otherwise advance our business. There can be no assurance that we will be able to manage our existing consultants or find other competent outside contractors and consultants on economically reasonable terms, if at all.

If we are not able to effectively expand our organization by hiring new employees and expanding our groups of consultants and contractors, we may not be able to successfully implement the tasks necessary to further develop our product candidates and, accordingly, may not achieve our research, development, and commercialization goals.

We have engaged in and may in the future engage in acquisitions or strategic partnerships, which may increase our capital requirements, dilute our stockholders, cause us to incur debt or assume contingent liabilities, and subject us to other risks.

We have in the past engaged in acquisitions and strategic partnerships, and we may engage in various acquisitions and strategic partnerships in the future, including licensing or acquiring complementary products, intellectual property rights, technologies, or businesses. For instance, in January 2018 we entered into the Takeda Collaboration Agreement, and in connection therewith we issued and sold to Takeda 4,214,559 shares of our common stock for an aggregate purchase price of \$110.0 million in February 2018. Additionally, on May 30, 2018, we exercised our buy-out option in connection with the F-star Collaboration Agreement and entered into a Purchase Agreement pursuant to which we acquired all of the outstanding shares of F-star Gamma. Any acquisition or strategic partnership may entail numerous risks, including:

- increased operating expenses and cash requirements;
- the assumption of indebtedness or contingent liabilities;
- the issuance of our equity securities which would result in dilution to our stockholders;
- assimilation of operations, intellectual property, products and product candidates of an acquired company, including difficulties associated with integrating new personnel;
- the diversion of our management's attention from our existing product programs and initiatives in pursuing such an acquisition or strategic partnership;
- retention of key employees, the loss of key personnel, and uncertainties in our ability to maintain key business relationships;
- risks and uncertainties associated with the other party to such a transaction, including the prospects of that party and their existing products or product candidates and regulatory approvals; and

[Table of Contents](#)

- our inability to generate revenue from acquired intellectual property, technology and/or products sufficient to meet our objectives or even to offset the associated transaction and maintenance costs.

In addition, if we undertake such a transaction, we may issue dilutive securities, assume or incur debt obligations, incur large one-time expenses and acquire intangible assets that could result in significant future amortization expense.

Our internal computer systems, or those used by our third-party research institution collaborators, CROs or other contractors or consultants, may fail or suffer security breaches.

Despite the implementation of security measures, our internal computer systems and those of our future CROs and other contractors and consultants may be vulnerable to damage from computer viruses and unauthorized access. Although to our knowledge we have not experienced any such material system failure or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations. For example, the loss of clinical trial data from completed, ongoing or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Likewise, we rely on our third-party research institution collaborators for research and development of our product candidates and other third parties for the manufacture of our product candidates and to conduct clinical trials, and similar events relating to their computer systems could also have a material adverse effect on our business. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or systems, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development and commercialization of our product candidates could be delayed.

Business disruptions could seriously harm our future revenue and financial condition and increase our costs and expenses.

Our operations, and those of our third-party research institution collaborators, CROs, CMOs, suppliers, and other contractors and consultants, could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics, and other natural or man-made disasters or business interruptions, for which we are partly uninsured. In addition, we rely on our third-party research institution collaborators for conducting research and development of our product candidates, and they may be affected by government shutdowns or withdrawn funding. The occurrence of any of these business disruptions could seriously harm our operations and financial condition and increase our costs and expenses. We rely on third-party manufacturers to produce and process our product candidates. Our ability to obtain clinical supplies of our product candidates could be disrupted if the operations of these suppliers are affected by a man-made or natural disaster or other business interruption.

All of our operations including our corporate headquarters are located in a single facility in South San Francisco, California. Damage or extended periods of interruption to our corporate, development or research facilities due to fire, natural disaster, power loss, communications failure, unauthorized entry or other events could cause us to cease or delay development of some or all of our product candidates. Although we maintain property damage and business interruption insurance coverage on these facilities, our insurance might not cover all losses under such circumstances and our business may be seriously harmed by such delays and interruption.

Our business is subject to economic, political, regulatory and other risks associated with international operations.

[Table of Contents](#)

Our business is subject to risks associated with conducting business internationally. Some of our suppliers and collaborative relationships are located outside the United States. Accordingly, our future results could be harmed by a variety of factors, including:

- economic weakness, including inflation, or political instability in particular non-U.S. economies and markets;
- differing and changing regulatory requirements in non-U.S. countries;
- challenges enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States;
- difficulties in compliance with non-U.S. laws and regulations;
- changes in non-U.S. regulations and customs, tariffs and trade barriers;
- changes in non-U.S. currency exchange rates and currency controls;
- changes in a specific country's or region's political or economic environment;
- trade protection measures, import or export licensing requirements or other restrictive actions by U.S. or non-U.S. governments;
- negative consequences from changes in tax laws;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- difficulties associated with staffing and managing international operations, including differing labor relations;
- potential liability under the FCPA, UK Bribery Act or comparable foreign laws; and
- business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods and fires.

These and other risks associated with our planned international operations may materially adversely affect our ability to attain profitable operations.

Our ability to use our net operating loss carryforwards and certain other tax attributes may be limited.

[Table of Contents](#)

As of December 31, 2017, we had federal net operating loss carryforwards of approximately \$134.1 million, and federal research and development tax credit carryforwards of approximately \$2.9 million which will begin to expire in 2035. Under Sections 382 and 383 of the United States Internal Revenue Code of 1986, as amended, or the Code, if a corporation undergoes an "ownership change" (generally defined as a greater than 50-percentage-point cumulative change (by value) in the equity ownership of certain stockholders over a rolling three-year period), the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change taxable income or taxes may be limited. As a result of our initial public offering ("IPO"), in December 2017 and recent private placements and other transactions that have occurred since our incorporation, we may have experienced such an ownership change. We may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which are outside our control. As a result, our ability to use our pre-change net operating loss carryforwards and other pre-change tax attributes to offset post-change taxable income or taxes may be subject to limitation.

Risks Related to Ownership of Our Common Stock

The market price of our common stock has been and may continue to be volatile, which could result in substantial losses for investors.

The trading price of our common stock has been and may continue to be highly volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this report, these factors include:

- the success of existing or new competitive products or technologies;
- the timing and results of clinical trials for our current product candidates and any future product candidates that we may develop;
- commencement or termination of collaborations for our product development and research programs;
- failure to achieve development, regulatory or commercialization milestones under our collaborations;
- failure or discontinuation of any of our product development and research programs;
- failure to develop our BBB platform technology;
- results of preclinical studies, clinical trials, or regulatory approvals of product candidates of our competitors, or announcements about new research programs or product candidates of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents, or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our research programs, clinical development programs, or product candidates that we may develop;
- the results of our efforts to develop additional product candidates or products;

[Table of Contents](#)

- actual or anticipated changes in estimates as to financial results, development timelines, or recommendations by securities analysts;
- announcement or expectation of additional financing efforts;
- sales of our common stock by us, our insiders, or other stockholders;
- expiration of market standoff or lock-up agreements;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in estimates or recommendations by securities analysts, if any, that cover our stock;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors; and
- general economic, industry, and market conditions.

In recent years, the stock market in general, and the market for pharmaceutical and biotechnology companies in particular, has experienced significant price and volume fluctuations that have often been unrelated or disproportionate to changes in the operating performance of the companies whose stock is experiencing those price and volume fluctuations. Broad market and industry factors may seriously affect the market price of our common stock, regardless of our actual operating performance. In the past, when the market price of a stock has been volatile, holders of that stock have instituted securities class action litigation against the company that issued the stock. If any of our stockholders were to bring a lawsuit against us, the defense and disposition of any such lawsuits could be costly and divert the time and attention of our management and harm our operating results, regardless of the merits of such a claim.

If securities analysts do not publish research or reports about our business or if they publish negative evaluations of our stock, the price of our stock and trading volume could decline.

The trading market for our common stock relies in part on the research and reports that industry or financial analysts publish about us or our business. If one or more of the analysts covering our business downgrade their evaluations of our stock, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price or trading volume to decline.

Raising additional capital may cause dilution to our existing stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.

We may seek additional capital through a combination of public and private equity offerings, debt financings, strategic partnerships and alliances and licensing arrangements. We, and indirectly, our stockholders, will bear the cost of issuing and servicing such securities. Because our decision to issue debt or equity securities in any future offering will depend on market conditions and other factors beyond our control, we cannot predict or estimate the amount, timing or nature of any future offerings. To the extent that we raise additional capital through the sale of equity or debt securities, your ownership interest will be diluted, and the terms may include liquidation or other preferences that adversely affect your rights as a stockholder. The incurrence of indebtedness would result in increased fixed payment obligations and could involve restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. Additionally, any future collaborations we enter into with third parties may provide capital in the near term but limit our potential cash flow and revenue in the future. If we raise additional funds through strategic partnerships and alliances and licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies or product candidates, or grant licenses on terms unfavorable to us.

Our principal stockholders and management own a significant percentage of our stock and will be able to exercise significant influence over matters subject to stockholder approval.

As of September 30, 2018, our directors, executive officers, holders of more than 5% of our outstanding stock and their respective affiliates beneficially own shares representing more than 50.0% of our outstanding common stock. As a result, these stockholders, if they act together, may significantly influence all matters requiring stockholder approval, including the election of directors and approval of significant corporate transactions. This concentration of ownership may have the effect of delaying or preventing a change in control of our company that our other stockholders may believe is in their best interests. This in turn could have a material adverse effect on our stock price and may prevent attempts by our stockholders to replace or remove the board of directors or management.

We are an “emerging growth company,” and the reduced disclosure requirements applicable to emerging growth companies may make our common stock less attractive to investors.

We are an “emerging growth company,” as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. We will remain an emerging growth company until the earliest to occur of: the last day of the fiscal year in which we have more than \$1.07 billion in annual revenue; the date we qualify as a “large accelerated filer,” with at least \$700 million of equity securities held by non-affiliates; the issuance, in any three-year period, by us of more than \$1.0 billion in non-convertible debt securities; and the last day of the fiscal year ending after the fifth anniversary of our initial public offering, or December 31, 2022. References herein to “emerging growth company” are intended to have the meaning associated with it in the JOBS Act. For so long as we remain an emerging growth company, we are permitted and plan to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, or SOX Section 404, not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor’s report providing additional information about the audit and the financial statements, reduced disclosure obligations regarding executive compensation, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved. As a result, the information we provide stockholders will be different than the information that is available with respect to other public companies. We cannot predict whether investors will find our common stock less attractive if we rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock, and our stock price may be more volatile.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards, and, therefore, are subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

We have incurred and will continue to incur increased costs as a result of operating as a public company, and our management has been and will continue to be required to devote substantial time to new compliance initiatives and corporate governance practices, including maintaining an effective system of internal controls over financial reporting.

[Table of Contents](#)

As a public company, and particularly after we are no longer an emerging growth company, we have incurred and will continue to incur significant legal, accounting, and other expenses that we did not incur as a private company. The SOX, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of NASDAQ, and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. We expect that we will need to hire additional accounting, finance, and other personnel in connection with our efforts to comply with the requirements of being a public company, and our management and other personnel will need to continue to devote a substantial amount of time towards maintaining compliance with these requirements. These requirements have and will continue to increase our legal and financial compliance costs and will make some activities more time-consuming and costly. We are currently evaluating these rules and regulations and cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. These rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

Pursuant to SOX Section 404, we will be required to furnish a report by our management on our internal control over financial reporting beginning with our second filing of an Annual Report on Form 10-K with the SEC after we become a public company. However, while we remain an emerging growth company, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with SOX Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants, adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented, and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk that we will not be able to conclude, within the prescribed timeframe or at all, that our internal control over financial reporting is effective as required by SOX Section 404. If we identify one or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

If we are unable to maintain effective internal controls, our business, financial position and results of operations could be adversely affected.

As a public company, we are subject to reporting and other obligations under the Securities Exchange Act of 1934, as amended, or the Exchange Act, including the requirements of SOX Section 404, which require annual management assessments of the effectiveness of our internal control over financial reporting. However, our auditors will not be required to formally attest to the effectiveness of our internal control over financial reporting pursuant to SOX Section 404 until we are no longer an emerging growth company if we continue to take advantage of the exemptions available to us through the JOBS Act.

The rules governing the standards that must be met for management to assess our internal control over financial reporting are complex and require significant documentation, testing and possible remediation to meet the detailed standards under the rules. During the course of its testing, our management may identify material weaknesses or deficiencies which may not be remedied in time to meet the deadline imposed by the Sarbanes-Oxley Act of 2002. These reporting and other obligations place significant demands on our management and administrative and operational resources, including accounting resources.

[Table of Contents](#)

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Our internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with accounting principles generally accepted in the United States. Any failure to maintain effective internal controls could have an adverse effect on our business, financial position and results of operations.

We have not paid and do not expect to pay any dividends for the foreseeable future. Any return on investment may be limited to the value of our common stock.

We have never paid cash dividends on our common stock and do not anticipate that we will pay any dividends in the foreseeable future. We currently intend to retain our future earnings, if any, to maintain and expand our existing operations. If we do not pay dividends, our common stock may be less valuable because a return on your investment will only occur if our stock price appreciates.

Delaware law and provisions in our charter documents might discourage, delay, or prevent a change in control of our company or changes in our management and, therefore, depress the trading price of our common stock.

Provisions in our amended and restated certificate of incorporation and amended and restated bylaws may discourage, delay, or prevent a merger, acquisition, or other change in control that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares of our common stock. These provisions may also prevent or frustrate attempts by our stockholders to replace or remove our management. Therefore, these provisions could adversely affect the price of our common stock. Among other things, our charter documents:

- establish that our board of directors is divided into three classes, Class I, Class II and Class III, with each class serving staggered three-year terms;
- provide that vacancies on our board of directors may be filled only by a majority of directors then in office, even though less than a quorum;
- provide that our directors may only be removed for cause;
- eliminate cumulative voting in the election of directors;
- authorize our board of directors to issue shares of preferred stock and determine the price and other terms of those shares, including preferences and voting rights, without stockholder approval;
- provide our board of directors with the exclusive right to elect a director to fill a vacancy or newly created directorship;
- permit stockholders to only take actions at a duly called annual or special meeting and not by written consent;
- prohibit stockholders from calling a special meeting of stockholders;
- require that stockholders give advance notice to nominate directors or submit proposals for consideration at stockholder meetings;
- authorize our board of directors, by a majority vote, to amend the bylaws; and
- require the affirmative vote of at least 66 2/3% or more of the outstanding shares of common stock to amend many of the provisions described above.

[Table of Contents](#)

In addition, Section 203 of the General Corporation Law of the State of Delaware, or DGCL, prohibits a publicly-held Delaware corporation from engaging in a business combination with an interested stockholder, generally a person which together with its affiliates owns, or within the last three years has owned, 15% of our voting stock, for a period of three years after the date of the transaction in which the person became an interested stockholder, unless the business combination is approved in a prescribed manner.

Any provision of our amended and restated certificate of incorporation, amended and restated bylaws, or Delaware law that has the effect of delaying or preventing a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our capital stock and could also affect the price that some investors are willing to pay for our common stock.

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware and the federal district courts of the United States of America will be the exclusive forums for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers, or employees.

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for:

- any derivative action or proceeding brought on our behalf;
- any action asserting a claim of breach of fiduciary duty;
- any action asserting a claim against us arising under the DGCL, our amended and restated certificate of incorporation, or our amended and restated bylaws; and
- any action asserting a claim against us that is governed by the internal-affairs doctrine.

Our amended and restated certificate of incorporation further provides that the federal district courts of the United States of America will be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act.

These exclusive-forum provisions may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers, or other employees, which may discourage lawsuits against us and our directors, officers, and other employees. If a court were to find either exclusive-forum provision in our amended and restated certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving the dispute in other jurisdictions, which could seriously harm our business.

ITEM 2. UNREGISTERED SALES OF EQUITY SECURITIES AND USE OF PROCEEDS

Recent Sales of Unregistered Securities

None.

Use of Proceeds from Registered Securities

On December 7, 2017, our Registration Statement on Form S-1 (File No. 333-221522) was declared effective by the SEC for our initial public offering of common stock. We started trading on The NASDAQ Global Select Market on December 8, 2017, and the transaction formally closed on December 12, 2017. In connection with the initial public offering, we sold an aggregate of 15,972,221 shares of common stock, including 2,083,333 shares sold pursuant to the underwriters' full exercise of their option to purchase additional shares, at a price to the public of \$18.00 per share. The aggregate offering price for shares sold in the offering was \$287.5 million. The joint book-running managers for the initial public offering were Goldman, Sachs & Co. LLC, Morgan Stanley & Co. LLC, and J.P. Morgan Securities LLC. After deducting underwriting discounts, commissions and offering expenses paid or payable by us of approximately \$23.2 million, the net proceeds from the offering were approximately \$264.3 million. No offering expenses were paid or are payable, directly or indirectly, to our directors or officers, to persons owning 10% or more of any class of our equity securities or to any of our affiliates.

There has been no material change in the planned use of proceeds from our initial public offering as described in our final prospectus filed with the SEC on December 8, 2017 pursuant to Rule 424(b)(4). We invested the funds received in short-term, interest-bearing investment-grade securities and government securities.

Issuer Purchases of Equity Securities

Not applicable.

ITEM 3. DEFAULTS UPON SENIOR SECURITIES

Not applicable.

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

[Table of Contents](#)

ITEM 5. OTHER INFORMATION

None.

ITEM 6. EXHIBITS

EXHIBIT INDEX

Exhibit Number	Description	Incorporated by Reference			
		Form	File No.	Number	Filing Date
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
10.1#	Amendment No. 3 to Development and Manufacturing Services Agreement between the Registrant and Lonza Sales AG, dated September 6, 2017, as amended by Amendment No. 1 on October 18, 2017 and Amendment No. 2 on January 18, 2018, dated July 2, 2018.				
10.2#	Amendment No. 4 to Development and Manufacturing Services Agreement between the Registrant and Lonza Sales AG, dated September 6, 2017, as amended by Amendment No. 1 on October 18, 2017, Amendment No. 2 on January 18, 2018 and Amendment No. 3 on July 2, 2018, dated August 30, 2018.				
31.1	Certification of Chief Executive Officer pursuant to Section 302 of the Sarbanes-Oxley Act.				
31.2	Certification of Chief Financial Officer pursuant to Section 302 of the Sarbanes-Oxley Act.				
32.1*	Certification of Chief Executive Officer pursuant to Section 906 of the Sarbanes-Oxley Act.				
32.2*	Certification of Chief Financial Officer pursuant to Section 906 of the Sarbanes-Oxley Act.				
101.INS	XBRL Instance Document.				
101.SCH	XBRL Taxonomy Extension Schema Document.				
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document.				
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document.				
101.LAB	XBRL Taxonomy Extension Label Linkbase Document.				
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document.				

* The certifications attached as Exhibits 32.1 and 32.2 that accompany this Quarterly Report on Form 10-Q are not deemed filed with the Securities and Exchange Commission and are not to be incorporated by reference into any filing of Denali Therapeutics Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, whether made before or after the date of this Form 10-Q, irrespective of any general incorporation language contained in such filing.

Portions of this exhibit have been omitted pursuant to a request for confidential treatment and this exhibit has been filed separately with the SEC.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

DENALI THERAPEUTICS INC.

Date: November 8, 2018

By: /s/ Ryan J. Watts
Ryan J. Watts, Ph.D.
President and Chief Executive Officer
(Principal Executive Officer)

Date: November 8, 2018

By: /s/ Steve E. Krognnes
Steve E. Krognnes
Chief Financial Officer and Treasurer
(Principal Financial and Accounting Officer)

Confidential

SPECIFIC TERMS IN THIS EXHIBIT HAVE BEEN REDACTED BECAUSE CONFIDENTIAL TREATMENT FOR THOSE TERMS HAS BEEN REQUESTED. THE REDACTED MATERIAL HAS BEEN SEPARATELY FILED WITH THE SECURITIES AND EXCHANGE COMMISSION, AND THE TERMS HAVE BEEN MARKED AT THE APPROPRIATE PLACE WITH THREE ASTERISKS [***].

AMENDMENT NO. 3

DEVELOPMENT AND MANUFACTURING SERVICES AGREEMENT

Dated 6th September 2017

Between

LONZA SALES AG

and

DENALI THERAPEUTICS INC.

Appendix A2 - Project Plan

Contents

[***]

[***]

Confidential

*** Certain information in this agreement has been omitted and filed separately with the Securities and Exchange Commission. [***] indicates that text has been omitted and is the subject of a confidential treatment request.

Confidential

THIS AMENDMENT is made the 2 day of July 2018

BETWEEN

LONZA SALES AG, of Muenchensteinerstrasse 38, Ch-4002 Basel, Switzerland (herein after referred to as "Lonza") and

DENALI THERAPEUTICS INC., of 151 Oyster Point Blvd, 2nd Floor, South San Francisco, CA 94080, U.S.A (hereinafter referred to as "Customer")

WHEREAS

- A. Customer and Lonza are Parties to a development and manufacturing services agreement dated 6th September 2017, as amended (the "Agreement"), pursuant to which Lonza is required to perform Services for Customer relating to the Cell Line and Product described (all terms as defined in the Agreement); and
- B. The Parties now wish to amend and supplement the terms of the Agreement

NOW THEREFORE it is agreed hereby by the parties to amend the Agreement and perform additional services as follows:

Confidential

Confidential

*** Certain information in this agreement has been omitted and filed separately with the Securities and Exchange Commission. *** indicates that text has been omitted and is the subject of a confidential treatment request.

B20869/HC/FA/21May18

Page 3 of 4

SPECIFIC TERMS IN THIS EXHIBIT HAVE BEEN REDACTED BECAUSE CONFIDENTIAL TREATMENT FOR THOSE TERMS HAS BEEN REQUESTED. THE REDACTED MATERIAL HAS BEEN SEPARATELY FILED WITH THE SECURITIES AND EXCHANGE COMMISSION, AND THE TERMS HAVE BEEN MARKED AT THE APPROPRIATE PLACE WITH THREE ASTERISKS [*].**

Amendment No. 4

to the

DEVELOPMENT AND MANUFACTURING SERVICES AGREEMENT

Dated 6th September 2017

Between

LONZA SALES AG

and

DENALI THERAPEUTICS INC.

Appendix A4 — Project Plan

THIS Amendment is made the 30th day of August 2018

BETWEEN

LONZA SALES AG, of Muenchensteinerstrasse 38, Ch-4002 Basel, Switzerland (herein after referred to as "Lonza") and

DENALI THERAPEUTICS INC., of 151 Oyster Point Blvd, 2nd Floor, South San Francisco, CA 94080, U.S.A (hereinafter referred to as "Customer")

WHEREAS

- A. Customer and Lonza are Parties to a development and manufacturing services agreement dated 6th September 2017, as amended (the "Agreement"), pursuant to which Lonza is required to perform Services for Customer relating to the Cell Line and Product described (all terms as defined in the Agreement); and
- B. The Parties now wish to amend and supplement the terms of the Agreement.

NOW THEREFORE in consideration of the mutual promises and covenants contained herein and other good and valuable consideration the sufficiency of which is acknowledged, it is hereby agreed by and between the Parties to amend the Agreement as follows:

- 1. The Project Plan attached to Amendment No. 4 and inserted as Appendix A4 to the Agreement shall be modified to add [***].
- 2. All capitalised terms used herein shall have the meanings set forth in the Agreement unless otherwise defined herein.
- 3. Save as herein provided all other terms and conditions of the Agreement shall remain in full force and "effect.

IN WITNESS WHEREOF the Parties have caused this Amendment No.4 to be executed by their representatives thereunto duly authorised as of the day and year first written.

Signed for and on behalf of /s/ Albert Pereda
LONZA SALES AG Senior Legal Counsel Title

Signed for and on behalf of /s/ Bart A. M. van Aarnhem
LONZA SALES AG Senior Legal Counsel Title

Signed for and on behalf of /s/ Mark Dresser 26 July 2018
DENALI THERAPEUTICS INC. Head of Dev. Sci. Title

Confidential

*** Certain information in this agreement has been omitted and filed separately with the Securities and Exchange Commission. [***] indicates that text has been omitted and is the subject of a confidential treatment request.

Appendix A2

Amendments to be made to the Project Plan

*** shall be added as below:

Contents

Confidential

*** Certain information in this agreement has been omitted and filed separately with the Securities and Exchange Commission. *** indicates that text has been omitted and is the subject of a confidential treatment request.

Confidential

*** Certain information in this agreement has been omitted and filed separately with the Securities and Exchange Commission. *** indicates that text has been omitted and is the subject of a confidential treatment request.

**CERTIFICATION OF PERIODIC REPORT UNDER SECTION 302 OF
THE SARBANES-OXLEY ACT OF 2002**

I, Ryan J. Watts, Ph.D., certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Denali Therapeutics Inc.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
 - (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
 - (b) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
 - (c) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
 - (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
 - (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: November 8, 2018

/s/ Ryan J. Watts

Ryan J. Watts, Ph.D.

President and Chief Executive Officer

**CERTIFICATION OF PERIODIC REPORT UNDER SECTION 302 OF
THE SARBANES-OXLEY ACT OF 2002**

I, Steve E. Krognes, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Denali Therapeutics Inc.;
2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;
3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;
4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:
 - (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;
 - (b) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and
 - (c) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and
5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):
 - (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and
 - (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: November 8, 2018

/s/ Steve E. Krognes

Steve E. Krognes

Chief Financial Officer and Treasurer

