Filed Pursuant to Rule 424(b)(4)
Registration File No. 333-221522

13,888,888 Shares

Common Stock

This is an initial public offering of shares of common stock by Denali Therapeutics Inc.

Prior to this offering, there has been no public market for our common stock. The initial public offering price is $18.00 per share.

Our common stock has been approved for listing on the NASDAQ Global Select Market under the symbol "DNLI."

We are an "emerging growth company" as defined under the federal securities laws and, as such, have elected to comply with certain reduced reporting requirements for this prospectus and may elect to do so in future filings.

Investing in our common stock involves risks. See the section titled "Risk Factors" beginning on page 13 to read about factors you should consider before buying shares of our common stock.

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

	Per Share	Total
Initial public offering price	$18.00	$ 249,999,984
Underwriting discounts(1)	$ 1.26	$ 17,499,999
Proceeds, before expenses, to us	$16.74	$ 232,499,985

(1) See the section titled "Underwriting" for additional information regarding compensation payable to the underwriters.

Certain of our existing stockholders, including one that beneficially owns more than 5% of our outstanding common stock, have agreed to purchase approximately 5,300,000 shares of our common stock in this offering at the initial public offering price. The underwriters will receive the same underwriting discounts and commissions on the shares purchased by these stockholders as they will on the other shares sold to the public in this offering.

To the extent that the underwriters sell more than 13,888,888 shares of common stock, the underwriters have the option to purchase up to an additional 2,083,333 shares from us at the initial public offering price less the underwriting discount.

The underwriters expect to deliver the shares against payment in New York, New York on December 12, 2017.

Goldman Sachs & Co. LLC **Morgan Stanley** **J.P. Morgan**

Evercore ISI

Prospectus dated December 7, 2017.

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Prospectus

Through and including January 1, 2018 (the 25th day after the date of this prospectus), all dealers effecting transactions in these securities, whether or not participating in this offering, may be required to deliver a prospectus. This is in addition to a dealer's obligation to deliver a prospectus when acting as an underwriter and with respect to an unsold allotment or subscription.

We and the underwriters have not authorized anyone to provide you any information other than that contained in this prospectus or in any free writing prospectus prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We and the underwriters are not making an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus is accurate only as of the date on the front cover of this prospectus. Our business, financial condition, results of operations and prospects may have changed since that date.

For investors outside of the United States: we have not and the underwriters have not done anything that would permit this offering or possession or distribution of this prospectus in any jurisdiction where action for that purpose is required, other than the United States. Persons outside of the United States who come into possession of this prospectus must inform themselves about, and observe any restrictions relating to, the offering of the shares of common stock and the distribution of this prospectus outside of the United States.

PROSPECTUS SUMMARY

This summary highlights selected information contained elsewhere in this prospectus and is qualified in its entirety by the more detailed information and financial statements included elsewhere in this prospectus. It does not contain all of the information that may be important to you and your investment decision. You should carefully read this entire prospectus, including the matters set forth under the sections titled "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our consolidated financial statements and related notes. In this prospectus, unless context requires otherwise, references to "we," "us," "our," "Denali," or "the company" refer to Denali Therapeutics Inc. See the section titled "Glossary" for definitions of key scientific and technical terms used in this prospectus.

Overview

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

Neurodegeneration represents one of the most significant unmet medical needs of our time, with few effective therapeutic options available for patients with Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, or ALS, and other neurodegenerative diseases. We believe the time is right to make a strong and ambitious effort to defeat neurodegeneration. Recent genetic insights are revealing the underlying biology of neurodegeneration and potential drug targets while enabling better patient selection, similar to how genetic insights have transformed the field of oncology. Identifying and selecting targets based on validated genetic drivers of neurodegeneration is a core principle of our strategy. The second core principle of our strategy is to develop medicines that effectively cross the blood-brain barrier, or BBB, and target the brain. We have engineered a proprietary BBB platform technology that we believe will enable therapeutically relevant concentrations of our product candidates in the brain. The third core principle of our strategy is to develop and use biomarkers for better patient selection and demonstration of target and pathway engagement of our product candidates. By executing this strategy with a team of experienced and passionately dedicated scientists and drug developers, we believe we can succeed in a field that has seen limited progress over the past several decades. We commenced operations in May 2015 and recently began our first clinical trials.

Our Team

We have assembled a team with deep scientific, clinical, business and leadership experience and expertise in biotechnology, and specifically in neurodegenerative diseases, who worked together at Genentech for many years prior to the founding of Denali. Our Co-Founder and Chief Executive Officer, Ryan J. Watts, Ph.D., is a world-leading drug developer and neuroscientist, with particular expertise in BBB therapeutic delivery. Dr. Watts most recently led the neuroscience research team at Genentech and has led multiple discovery teams, including programs in Alzheimer's disease, Parkinson's disease and ALS. Our Co-Founder and Chief Operating Officer, Alexander O. Schuth, M.D., held various operational and leadership roles at Genentech for nearly ten years, including leading the partnering groups for neuroscience as well as technology innovation and diagnostics. Dr. Schuth has led more than 35 partnering transactions and a clinical stage development program. Our Co-Founder and director, Marc Tessier-Lavigne, Ph.D., is a world-leading neuroscientist, was formerly Chief Scientific Officer at Genentech and serves as President of Stanford University. Carole Ho, M.D., our Chief Medical Officer, brings over a decade of clinical development experience, most recently as Vice President, Non-Oncology Early Clinical Development at Genentech. Dr. Ho has overseen or contributed to more than ten IND filings and three drug approvals. Our Chief Financial

Officer, Steve E. Krognes, brings over two decades of operational and corporate finance experience, most recently serving six years as Chief Financial Officer and member of the Executive Committee at Genentech. Mr. Krognes has led more than 40 strategic deals and led or contributed to several capital raising transactions.

Our leadership team is joined by approximately 125 employees, approximately two-thirds of whom hold Ph.D. or M.D. degrees. Together, they bring expertise across relevant disciplines, including neuroscience, BBB biology, genetics, oncology, immunology, translational science, antibody engineering, chemistry and biomarker development.

To complement our internal capabilities, we have entered into arrangements with biopharmaceutical companies such as Genentech and F-star, numerous leading academic institutions such as Harvard University, Massachusetts General Hospital, Washington University in St. Louis, the University of California, San Diego and Vlaams Instituut voor Biotechnologie, foundations such as the Michael J. Fox Foundation and patient-focused data companies such as 23andMe and Patients Like Me to gain access to new product candidates, deepen our scientific understanding of certain areas of biology and enable and accelerate the development of our programs. We believe that accessing external innovation is important to our success, and we plan to remain active in accessing external innovation through business development activities.

Our Strategy

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 blood-brain barrier 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.

We believe that the application of these principles will significantly increase the probability of success and will accelerate the timing to bring effective therapeutics to patients with neurodegenerative diseases.

Degenogenes

Since 2007, the number of genetic associations discovered in neurodegenerative diseases has grown rapidly, with more than 100 genes associated with Alzheimer's disease, Parkinson's disease and ALS collectively. As the cost of genome sequencing has decreased, there has been an increase in the discovery of genetic mutations that have been linked to neurodegeneration (Figure A).

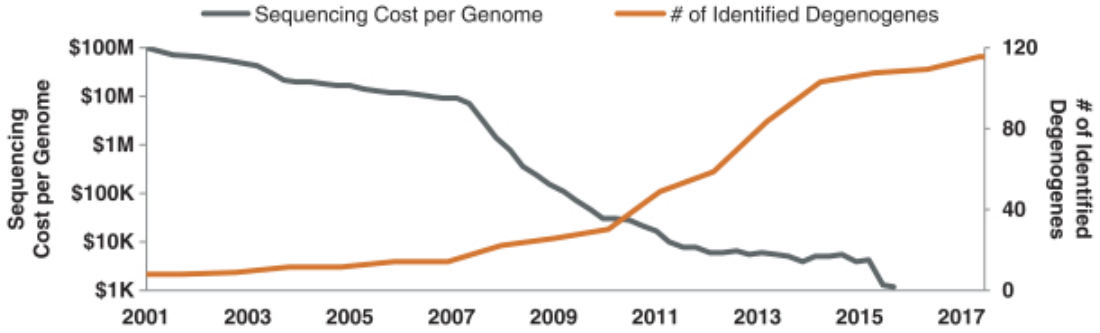


Figure A: This figure shows the increasing number of identified degenogenes linked to Alzheimer's disease, Parkinson's disease and ALS from 2001 to 2017 and the declining cost of genome sequencing from 2001 to October 2015 (the latest date for which we have data). There has been a dramatic reduction in the cost of DNA sequencing which has recently contributed to the discovery of numerous genetic mutations that have been linked to Alzheimer's disease, Parkinson's disease and ALS.

The degenogenes directly point to important disease pathways that are disrupted in neurodegeneration and are our scientific foundation for identifying and pursuing promising targets for drug development. We have chosen to initially focus on three such pathways:

- **Lysosomal Function**: Dysfunction of the lysosomal system is associated with several neurodegenerative diseases, including Parkinson's disease and neurodegeneration in the context of lysosomal storage diseases, or LSDs. Degenogenes linked to lysosomal function include LRRK2, aSyn and lysosomal enzymes, including IDS and GBA.
- **Glial Biology**: Degenogenes implicate immune dysfunction in the brains of patients with Alzheimer's disease and other neurodegenerative diseases. These genes include TREM2 and numerous other genes that are highly expressed in inflamed microglia, the resident immune cells of the brain. We believe the impact of immune modulation in neurodegeneration is a promising approach to treating disease. Specifically, RIPK1, a kinase downstream of the TNF receptor pathway, is overactive in inflamed microglia and several other cells in the brain.
- **Cellular Homeostasis**: Defects in protein or RNA homeostasis lead to the death of neurons and dysfunction of the nervous system. This includes spreading of protein aggregates resulting in proteinopathy in Alzheimer's and Parkinson's diseases. The clearance of macromolecules in the brain is particularly susceptible to imbalances that result in aggregation and degeneration in nerve cells. Degenogenes linked to cellular homeostasis include APP, Tau and APOE.

BBB Platform Technology

Our proprietary BBB platform technology is designed to effectively transport antibodies (antibody transport vehicle, or ATV) and enzymes (enzyme transport vehicle, or 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 (Figure B). In a mouse model across three studies designed to show proof of concept for the ATV platform, an antibody engineered with our ATV technology has demonstrated an average 20-fold greater brain penetration than a control antibody not enabled by this technology. In addition, initial data from an ongoing study in nonhuman primates designed to show proof of concept for the ATV platform demonstrates a robust and sustained pharmacodynamic effect in the brain after intravenous dosing of an ATV-enabled antibody, while a standard antibody had minimal pharmacodynamic effect. The improvement in brain exposure may enable therapeutically relevant concentrations of our ATV antibody product candidates in the brain, making them potentially superior to traditional monoclonal antibody therapeutics.

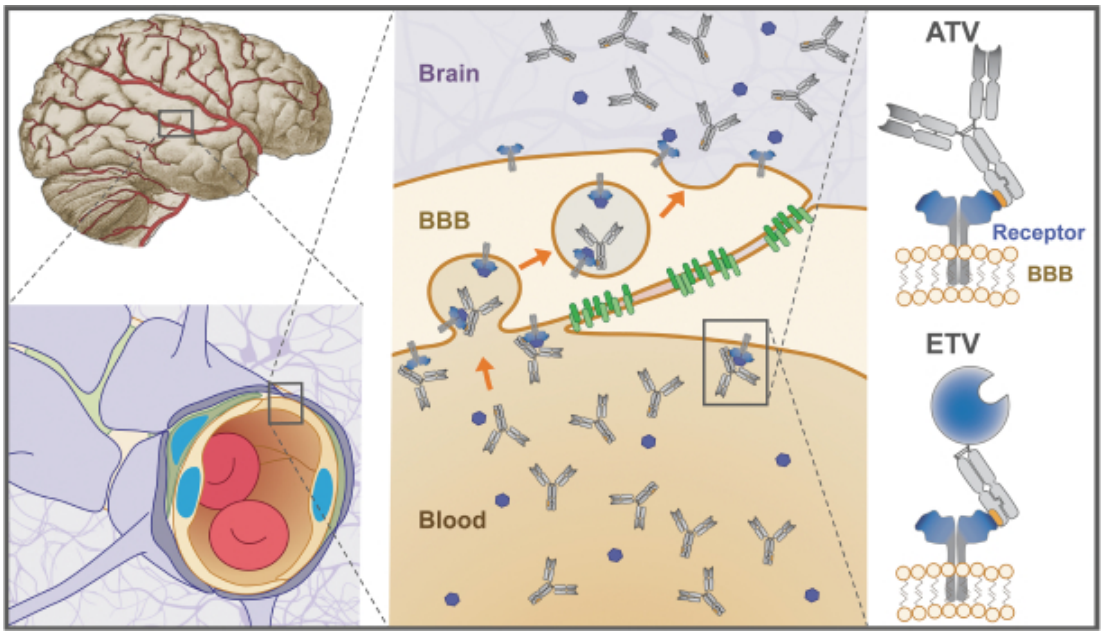


Figure B: Engineering brain delivery. Schematic of the ATV and ETV technologies, designed to cross the BBB through receptor-mediated transcytosis, leveraging endogenous receptors expressed on endothelial cells in the vasculature of the brain.

Biomarkers

As part of our strategy, we are developing proprietary reagents and assays to enable biomarkers for each of our core programs. These biomarkers, which are relevant for both animal models and human trials, are critical for patient selection, predicting and measuring target engagement, supporting dose selection and enabling decisions on progression of product candidates to the next phase of development. We have identified target engagement biomarkers for all six of our core programs. When practicable, we are developing patient selection biomarkers for our programs to enable identification of patients with the relevant disease biology and stage of disease likely to benefit from targeted therapy in order to increase the likelihood of success of clinical trials. Ultimately, by reducing the number of patients that are likely to experience a low treatment response, we expect to positively impact market acceptance of these targeted therapies driven by high and meaningful response rates within the targeted population as defined by the patient selection biomarkers. In certain indications, regulatory approval may limit the market of a product candidate to target patient populations when patient selection biomarkers are used.

In these indications, regulatory authorities may require us to run additional clinical trials prior to expanding the label for approval that includes a broader patient population.

Our Programs

We have a focused yet diversified portfolio that currently consists of six core and five seed programs. Our most advanced program targets LRRK2 for the treatment of Parkinson's disease and has a product candidate currently in Phase 1 development. Our next most advanced program targets RIPK1 for the treatment of Alzheimer's disease and ALS and currently has a product candidate in IND-enabling studies with a CTA filing planned for early 2018. In addition, we have four core programs in preclinical development that use our proprietary BBB platform technology.

Program Target	Drug Candidate	Therapeutic Modality	Disease Indication	Preclinical Development	Clinical Development			Biomarker		
					Phase I	Phase II	Phase III	Preclinical Target Engagement	Clinical Target Engagement	Patient Selection
Lysosomal Function Pathway										
LRRK2	DNL201	Small Molecule	Parkinson's disease	Phase 1				✓	✓	✓
	DNL151	Small Molecule	Parkinson's disease	CTA accepted						
Alpha-Synuclein	ATV:aSyn	Antibody	Parkinson's disease, DLB, MSA	Preclinical				✓	●	●
Iduronate 2-sulfatase	ETV:IDS	Enzyme	MPS II (Hunter Syndrome)	Preclinical				✓	✓	✓
Glial Biology Pathway										
RIPK1	DNL747	Small Molecule	Alzheimer's disease, ALS	IND-Enabling				✓	✓	●
TREM2	ATV:TREM2	Antibody	Alzheimer's disease	Preclinical				✓	●	●
Cellular Homeostasis Pathway										
BACE1/TAU	ATV:BACE1/Tau	Antibody	Alzheimer's disease	Preclinical				✓	✓	✓

ATV: Antibody Transport Vehicle
ETV: Enzyme Transport Vehicle
ALS: Amyotrophic Lateral Sclerosis
DLB: Dementia with Lewy Bodies
MPS II: Mucopolysaccharidosis type II
MSA: Multiple System Atrophy

✓ Validated biomarker available
● Biomarker in development

Our lead LRRK2 product candidates, DNL201 and DNL151, are potent, selective and brain penetrant small molecule inhibitors of LRRK2. LRRK2 regulates lysosomal genesis and function, which is impaired in Parkinson's disease and may be restored by LRRK2 inhibition. Mutations in the LRRK2 gene are the most frequent genetic cause of Parkinson's disease and a major driver of lysosomal dysfunction, which contributes to the formation of Lewy body protein aggregates and neurodegeneration. DNL201 is currently in a single and multiple ascending dose study in healthy volunteers. The FDA placed DNL201 on a partial clinical hold in order to impose an exposure cap on our Phase 1 study based on preclinical toxicity study findings. With the current exposure cap, we are able to dose to an exposure that we believe will be sufficient to inhibit LRRK2 50% on average over the dosing period and should effectively normalize LRRK2 kinase activity. If the exposure cap is not lifted in our Phase 1 clinical trial, we will not be able to evaluate doses and exposures that would potentially achieve higher degrees of LRRK2 kinase inhibition, which may negatively impact the development of DNL201. We expect data from this study in the first half of 2018. We submitted a CTA for DNL151 to the Netherlands Health Authority in October 2017 and it was accepted in November 2017. After completion of the Phase 1 clinical trials for DNL201 and DNL151, we plan to progress one of DNL201 or DNL151 into a Phase 1b study in LRRK2 mutation-carrying Parkinson's disease patients.

Our lead RIPK1 product candidate, DNL747, is a potent, selective and brain penetrant small molecule inhibitor of RIPK1 for Alzheimer's disease and ALS. Microglia are the resident immune cells of the brain and play a significant role in neurodegeneration. RIPK1 activation in microglia results in production of a number of pro-inflammatory cytokines that can cause tissue damage. Preliminary data from our GLP toxicity studies, including our 28-day GLP safety studies in cynomolgus monkeys and

rats, support advancing DNL747 to clinical testing. Immune-mediated histopathology findings were observed in our 28-day GLP study in cynomolgus monkeys, but we believe the projected safety margins will allow us to achieve DNL747 exposures that allow us to explore a robust pharmacodynamic range in humans. We plan to submit a CTA for DNL747 in early 2018 and initiate a Phase 1 clinical trial in healthy volunteers in the first half of 2018.

Our four other core programs all leverage our proprietary BBB platform technology to deliver antibody-based or enzyme-based therapies to the brain. Our three antibody programs are against known targets including aSyn, TREM2 and a bispecific therapeutic agent against both BACE1 and Tau. Our BACE1 and Tau program is an example of combination therapy, which we believe holds significant promise in developing effective therapies in neurodegenerative diseases. We believe each of these programs has characteristics that may allow for them to be best in class. Our fourth program is an enzyme replacement therapy for MPS II patients in which we deliver IDS to the brain. Neurodegeneration is a hallmark of MPS II patients that is not addressed by current enzyme replacement therapies, which fail to reach the brain.

We have development and commercialization rights to all of our core programs.

Risks Associated with Our Business

Our business is subject to numerous risks and uncertainties that you should consider before investing in our company. These risks are described more fully in the section titled “Risk Factors” in this prospectus. These risks include, but are not limited to, the following:

- We are in the early stages of clinical drug development and have a very limited operating history and no products approved for commercial sale.
- 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.
- 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 revenue or be profitable.
- If we fail to obtain additional financing, we may be unable to complete the development and, if approved, commercialization of our product candidates.
- 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 may not be successful in our efforts to continue to create a pipeline of product candidates or to develop commercially successful products.
- We have concentrated our research and development efforts on the treatment of neurodegenerative diseases, a field that has seen limited success in drug development.
- 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.
- 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.
- The regulatory approval processes of the FDA, EMA and comparable foreign regulatory authorities are lengthy, time consuming and inherently unpredictable.

- 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 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.
- 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.

Corporate Information

We were incorporated in Delaware in 2013. Our principal executive offices are located at 151 Oyster Point Blvd., 2nd Floor, South San Francisco, California 94080. Our telephone number is (650) 866-8548. Our website address is www.denalitherapeutics.com. Information contained on our website is not incorporated by reference into this prospectus, and it should not be considered to be part of this prospectus.

We use Denali Therapeutics®, the Denali Therapeutics logo, and other marks as trademarks in the United States and other countries. This prospectus contains references to our trademarks and service marks and to those belonging to other entities. Solely for convenience, trademarks and trade names referred to in this prospectus, including logos, artwork and other visual displays, may appear without the ® or ™ symbols, but such references are not intended to indicate in any way that we will not assert, to the fullest extent under applicable law, our rights or the rights of the applicable licensor to these trademarks and trade names. We do not intend our use or display of other entities' trade names, trademarks or service marks to imply a relationship with, or endorsement or sponsorship of us by, any other entity.

Implications of Being an Emerging Growth Company

We are an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, as amended, or 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. As a result of this status, we have taken advantage of reduced reporting requirements in this prospectus and may elect to take advantage of other reduced reporting requirements in our future filings with the SEC. In particular, in this prospectus, we have provided only two years of audited financial statements and have not included all of the executive compensation related information that would be required if we were not an emerging growth company. In addition, the JOBS Act provides that an emerging growth company may take advantage of an extended transition period for complying with new or revised accounting standards, delaying the adoption of these accounting standards until they would apply to private companies. We have irrevocably elected not to avail ourselves of this exemption and, as a result, upon completion of this offering we will adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required for other public companies that are not emerging growth companies.

THE OFFERING

Common stock offered by us	13,888,888 shares
Common stock to be outstanding after this offering	87,979,475 shares (or 90,062,808 shares if the underwriters exercise their option to purchase additional shares in full)
Underwriters' option to purchase additional shares of common stock from us	2,083,333 shares
Use of proceeds	We estimate that the net proceeds from our issuance and sale of 13,888,888 shares of our common stock in this offering will be approximately $229.0 million, based upon the initial public offering price of $18.00 per share, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us. If the underwriters exercise their option to purchase additional shares in full, we estimate that our net proceeds will be approximately $263.9 million. We currently anticipate that we will use the net proceeds from this offering, together with our existing resources, through 2019 as follows: (1) to fund the costs of Phase 1 trials in healthy volunteers for each of DNL201 and DNL151 and a Phase 1b study in LRRK2 mutation-carrying Parkinson's disease patients, as well as preparation for a potential future Phase 2 clinical trial; (2) to fund the costs to advance our RIPK1 program through Phase 1 and early Phase 2 clinical development, substantially represented by the planned Phase 1 clinical trial in healthy volunteers, including a cohort in Alzheimer's disease patients, for DNL747, a Phase 2a clinical trial in ALS patients and a Phase 2a clinical trial in Alzheimer's disease patients; (3) to optimize and broaden our ATV and ETV platform technologies and to advance our four core antibody and enzyme replacement programs through preclinical development and IND-enabling activities; (4) if we exercise our option to acquire all outstanding shares of F-star Gamma, to fund the initial exercise payments; and (5) the remainder to fund seed programs, general research and development activities, working capital and other general corporate activities. See the section titled "Use of Proceeds" for additional information.
NASDAQ Global Select Market trading symbol	"DNLI"

The number of shares of our common stock to be outstanding after this offering is based on the 74,090,587 shares of our common stock outstanding as of September 30, 2017 (including convertible preferred stock on an as-converted basis, as well as 1,764,705 shares of our Series B-2 convertible preferred stock issued after September 30, 2017), and excludes the following:

- 6,179,687 shares of common stock issuable upon exercise of options to purchase shares of our common stock outstanding as of September 30, 2017, at a weighted-average exercise price of $3.06 per share;
- 194,000 shares of common stock issuable upon exercise of options to purchase shares of our common stock that were granted after September 30, 2017, at a weighted-average exercise price of $11.64 per share;
- 81,164 shares of common stock to be issued in connection with our acquisition of Incro Pharmaceuticals;
- 7,379,238 shares of common stock reserved for future issuance under our stock-based compensation plans, consisting of:
  - 169,238 shares of common stock reserved for future issuance under our 2015 Stock Incentive Plan, as amended, or our 2015 Plan, which shares will be added to the shares to be reserved under our 2017 Equity Incentive Plan, or our 2017 Plan;
  - 6,210,000 shares of common stock reserved for future issuance under our 2017 Plan (excluding the 169,238 shares to be transferred from our 2015 Plan), which became effective in connection with this offering, and any additional shares that become available under our 2017 Plan pursuant to provisions thereof that automatically increase the share reserve under the plan each year, as more fully described in the section titled “Executive Compensation—Employee Benefit and Stock Plans;” and
  - 1,000,000 shares of common stock reserved for future issuance under our 2017 Employee Stock Purchase Plan, or ESPP, which became effective in connection with this offering, and any additional shares that become available under our ESPP pursuant to provisions thereof that automatically increase the share reserve under the plan each year, as more fully described in the section titled “Executive Compensation—Employee Benefit and Stock Plans.”

Unless otherwise indicated, this prospectus reflects and assumes the following:

- a 4-for-1 reverse stock split of our common stock and convertible preferred stock effected on November 28, 2017;
- no exercise of outstanding options;
- no exercise by the underwriters of their option to purchase up to an additional 2,083,333 shares of our common stock from us;
- the conversion of all outstanding shares of our convertible preferred stock into an aggregate of 60,365,020 shares of our common stock, which will occur immediately prior to the closing of this offering; and
- the filing and effectiveness of our amended and restated certificate of incorporation and the effectiveness of our amended and restated bylaws, which will occur immediately prior to the closing of this offering.

Certain of our existing stockholders, including one that beneficially owns more than 5% of our outstanding common stock, have agreed to purchase approximately 5,300,000 shares of our common

stock in this offering at the initial public offering price. The underwriters will receive the same underwriting discounts and commissions on the shares purchased by these stockholders as they will on the other shares sold to the public in this offering.

SUMMARY CONSOLIDATED FINANCIAL DATA

The following tables summarize our consolidated financial data for the periods and as of the dates indicated. We have derived the consolidated statements of operations and comprehensive loss data for the years ended December 31, 2015 and 2016 from our audited consolidated financial statements included elsewhere in this prospectus. The consolidated statements of operations and comprehensive loss data for the nine months ended September 30, 2016 and 2017 and the balance sheet data as of September 30, 2017 have been derived from our unaudited interim condensed consolidated financial statements included elsewhere in this prospectus and have been prepared in accordance with generally accepted accounting principles in the United States of America on the same basis as the annual audited consolidated financial statements and, in the opinion of management, the unaudited data reflects all adjustments, consisting only of normal recurring adjustments, necessary for the fair presentation of the financial information in those statements. Our historical results are not necessarily indicative of results that may be expected in the future, and results for the nine months ended September 30, 2017 are not necessarily indicative of the results to be expected for the full year ending December 31, 2017. You should read the following summary consolidated financial data together with our consolidated financial statements and the related notes appearing elsewhere in this prospectus and the information in the sections titled “Selected Consolidated Financial Data” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations.”

	Year Ended December 31,		Nine Months Ended September 30,	
	2015	2016	2016	2017
	(in thousands, except share and per share amounts)			
Consolidated Statements of Operations and Comprehensive Loss Data:				
Operating expenses:				
Research and development	$ 11,571	$ 75,702	$ 58,972	$ 55,989
General and administrative	5,108	11,731	8,685	10,611
Total operating expenses	16,679	87,433	67,657	66,600
Loss from operations	(16,679)	(87,433)	(67,657)	(66,600)
Interest income (expense), net	(109)	781	359	1,302
Net loss	(16,788)	(86,652)	(67,298)	(65,298)
Other comprehensive income (loss)	—	(373)	(131)	136
Comprehensive loss	$ (16,788)	$ (87,025)	$ (67,429)	$ (65,162)
Net loss per share, basic and diluted (1)	$ (5.58)	$ (13.49)	$ (11.43)	$ (6.77)
Weighted-average number of shares outstanding, basic and diluted (1)	3,006,379	6,424,720	5,888,385	9,643,686
Pro forma net loss per share, basic and diluted (unaudited) (1)		$ (1.77)		$ (0.96)
Pro forma weighted-average common shares outstanding, basic and diluted (unaudited) (1)		48,924,244		68,244,028

(1) See the consolidated statements of operations and Note 12 to our consolidated financial statements, and the condensed consolidated statements of operations and Note 9 to our unaudited condensed consolidated financial statements, for further details on the calculation of net

loss per share, basic and diluted, and the weighted-average number of shares used in the computation of the per share amounts and unaudited pro forma information.

	As of September 30, 2017		
	Actual	Pro Forma (1)	Pro Forma As Adjusted (2)
		(in thousands) (unaudited)	
Consolidated Balance Sheet Data:			
Cash, cash equivalents and marketable securities	$ 190,776	$ 220,676	$ 449,676
Working capital (3)	178,089	207,989	436,989
Total assets	210,309	240,209	469,209
Total liabilities	17,172	17,172	17,172
Convertible preferred stock	348,673	—	—
Accumulated deficit	(168,810)	(168,810)	(168,810)
Total stockholders' equity (deficit)	(155,536)	223,037	452,037

(1) The pro forma balance sheet data in the table above reflects the conversion of our outstanding shares of our convertible preferred stock into 60,365,020 shares of our common stock, which will occur immediately prior to the closing of this offering and the filing and effectiveness of our amended and restated certificate of incorporation. This includes the impact to assets and stockholders' equity of 1,764,705 shares issuable upon conversion of our Series B-2 convertible preferred stock.

(2) The pro forma as adjusted balance sheet data in the table above reflects the pro forma adjustments described in footnote (1) above plus the sale and issuance by us of shares of our common stock in this offering, based upon the initial public offering price of $18.00 per share, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

(3) We define working capital as current assets less current liabilities. See our condensed consolidated financial statements for further details regarding our current assets and current liabilities.

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 prospectus, including our financial statements and the related notes and the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations" in this prospectus, before deciding whether to invest in our common stock. 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.

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, or ALS. We commenced operations in May 2015, have no products approved for commercial sale and have not generated any revenue. Drug development is a highly uncertain undertaking and involves a substantial degree of risk. We have only recently begun a Phase 1 clinical trial for our most advanced product candidate, DNL201, which is in our LRRK2 core program, 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 $86.7 million and $16.8 million for the years ended December 31, 2016 and 2015, respectively, and $65.3 million for the nine months ended September 30, 2017. As of September 30, 2017, we had an accumulated deficit of $168.8 million.

We have invested significant financial resources in research and development activities, including for our preclinical and clinical product candidates and our blood-brain barrier, or 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;

- continue the development of our BBB platform technology;
- 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;
- 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 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;
- 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 sale of equity securities. We are currently advancing one

product candidate, DNL201, 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 beyond the net proceeds of this offering.

As of September 30, 2017, we had $190.8 million in cash, cash equivalents and marketable securities. We estimate that our net proceeds from this offering will be approximately $229.0 million, based on the initial public offering price of $18.00 per share, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us. 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 11 programs. We designate certain programs as core programs and others as seed programs. Together, these programs require significant capital investment. We currently have six core programs which are at various stages of preclinical and early clinical development, and our seed programs are in the research, discovery and preclinical stages of 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 three 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. We regularly review the designation of each program as core or seed, and terminate those programs which do not meet our development criteria.

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.

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, in a Phase 1 clinical trial in healthy volunteers in the United States. 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.

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 beyond the net proceeds of this offering 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 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:

- 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 contract research organizations, or 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, or 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 contract manufacturing organization, or CMO, or by us, and delays or failure by our CMOs or us to make any necessary changes to such manufacturing process; and
- 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, which is currently in a Phase 1 clinical trial in healthy volunteers in the United States, is subject to a partial clinical hold issued by the FDA due to adverse clinical signs (e.g. severe hypoactivity and prostration) observed in our 10-day oral dose ranging pilot toxicity studies designed to define the maximum tolerated dose of DNL201 in rats. This partial clinical hold relates to the FDA's decision to impose an exposure cap in our Phase 1 healthy volunteer clinical trial. The partial clinical hold prohibits evaluation of DNL201 above a specific exposure level. The FDA may re-evaluate the exposure cap for this trial, and may potentially raise it, based on the safety and tolerability data generated by the trial as well as data supporting the monitorability of the effects of the trial. We cannot assure you that the FDA will deem our response to be a complete response or that it will determine to lift or change the exposure cap imposed, and ultimately lift this partial clinical hold. If the FDA does not lift or change the exposure cap currently imposed, this may negatively impact the development of DNL201 if we determine that we must achieve higher degrees of LRRK2 kinase inhibition than what can be achieved with the current exposure cap. If we make such determination and the FDA does not lift the exposure cap, we may be unable to continue or complete our clinical trial of DNL201. Any inability to continue or complete our clinical trial of DNL201, as a result of the partial clinical hold or otherwise, will delay or terminate our clinical development plans for DNL201, may require us to incur additional clinical development costs and could impair our ability to ultimately obtain FDA approval for DNL201. Furthermore, we proactively proposed

an interim exposure cap in our planned Phase 1 healthy volunteer clinical trial for DNL151. We observed toxicity at high doses in cynomolgus monkeys in our 28-day GLP safety study of our lead RIPK1 product candidate, DNL747, and we are in the process of completing our analysis of the data from such study. Adverse findings in such preclinical studies could result in the regulatory authorities imposing, or us proactively proposing, an exposure cap in our planned Phase 1 clinical trial for DNL747. 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;
- 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.

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, Pfizer, 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.

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.

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, or 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.

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.

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.

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.

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 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.

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 candidate, DNL201, is currently our only clinical stage product candidate. In June 2017, we initiated a Phase 1 clinical trial of DNL201 in healthy volunteers in the United States and, to date, it has been well tolerated. However, adverse events and other side effects may result from higher dosing, repeated dosing and/or longer-term exposure to DNL201 and could lead to delays and/or termination of the development of this product candidate.

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;
- 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 to assure safe use;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

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.

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
- 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.

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;
- 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.

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.

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.

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 a collaboration with F-star, among 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;
- 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;
- 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 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 undergo a change of control and the 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;
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates or 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.

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.

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 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, 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 or that cover the composition of matter of our DNL151 product candidate, which is in our LRRK2 core program. In addition, we do not own or in-license any issued patents covering the Fc domain portion of our BBB platform technology that binds to transferrin receptor, or any issued patents that cover 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.

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 an exclusive 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. In addition, in August 2016, we entered into a collaboration with UK-based F-star, a biopharmaceutical company developing novel bispecific antibodies, focused on research and development of our BBB platform technology. The agreement with F-star includes certain non-exclusive licenses to F-star's modular antibody technology to research and develop certain antibodies, as well as options for us to obtain exclusive rights to develop and commercialize certain antibodies by exercising an option to obtain certain exclusive licenses or to buy-out all of the outstanding shares of F-star Gamma. See the section titled "Business—Licenses and Collaborations—F-star License and Collaboration Agreement" for additional information. However, we will not obtain exclusive rights to commercialize and exploit such antibodies unless we exercise our options to obtain such exclusive rights within specified periods of time. If we do not exercise our options with respect to a particular antibody in a timely manner or at all, or fail to satisfy any conditions upon which our options are contingent, F-star may offer such exclusive rights to other third parties. In addition, F-star may breach our agreement and attempt to license such patents and patent applications to other third parties, including our competitors, before or after we exercise our options. If we are unable to secure exclusive rights to F-star's modular antibody technology to commercialize and exploit our antibodies, our competitive position, business, financial condition, results of operations, and prospects may be materially harmed.

Our agreement with F-star and other license agreements may not provide exclusive rights to use the 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.

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.

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.

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.

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.

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.

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.

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.

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, 2017, we had approximately 125 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.

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.

If we engage in acquisitions or strategic partnerships, this 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 we may engage in various acquisitions and strategic partnerships in the future, including licensing or acquiring complementary products, intellectual property rights, technologies, or businesses. 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
- 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.

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 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.

As of December 31, 2016, we had federal net operating loss carryforwards of approximately $65.4 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 most recent private placements and other transactions that have occurred since our incorporation, we may have experienced, and, in connection with this offering, may experience, 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 This Offering and Ownership of Our Common Stock

We do not know whether a market will develop for our common stock or what the market price of our common stock will be, and, as a result, it may be difficult for you to sell your shares of our common stock.

Before this offering, there was no public trading market for our common stock. If a market for our common stock does not develop or is not sustained, it may be difficult for you to sell your shares of common stock at an attractive price or at all. We cannot predict the prices at which our common stock will trade. It is possible that in one or more future periods our results of operations and progression of our product pipeline may not meet the expectations of public market analysts and investors, and, as a result of these and other factors, the price of our common stock may fall.

The market price of our common stock may be volatile, which could result in substantial losses for investors purchasing shares in this offering.

The initial public offering price for our common stock was determined through negotiations with the underwriters. This initial public offering price may differ from the market price of our common stock after the offering. As a result, you may not be able to sell your common stock at or above the initial public offering price. Some of the factors that may cause the market price of our common stock to fluctuate 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 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;
- 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;
- general economic, industry, and market conditions; and
- the other factors described in this “Risk Factors” section.

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. These fluctuations may be even more pronounced in the trading market for our stock shortly following this offering. Following periods of such volatility in the market price of a company’s securities, securities class action litigation has often been brought against that company. Because of the potential volatility of our stock price, we may become the target of securities litigation in the future. Securities litigation could result in substantial costs and divert management’s attention and resources from our business.

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 could decline.

The trading market for our common stock will rely in part on the research and reports that industry or financial analysts publish about us or our business. We do not currently have and may never obtain research coverage by industry or financial analysts. If no or few analysts commence coverage of us, the trading price of our stock could decrease. Even if we do obtain analyst coverage, 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 to decline.

A significant portion of our total outstanding shares is restricted from immediate resale but may be sold into the market in the near future, which could cause the market price of our common stock to decline significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. These sales, upon the expiration of the market standoff and lock-up agreements, the early release of these agreements, or the perception in the market that the holders of a large number of shares of common stock intend to sell shares, could reduce the market price of our common stock. After this offering and after giving effect to the conversion of all outstanding shares of our convertible

preferred stock into 60,365,020 shares of our common stock upon the closing of this offering (including 1,764,705 additional shares of our common stock issuable upon conversion of our Series B-2 convertible preferred stock issued after September 30, 2017), we will have 87,979,475 shares of common stock outstanding based on 13,725,567 shares of our common stock outstanding as of September 30, 2017. Of these shares, the 13,888,888 shares we are selling in this offering may be resold in the public market immediately, unless purchased by our affiliates. The remaining 74,090,587 shares, or 84.2% of our outstanding shares after this offering, are currently prohibited or otherwise restricted under securities laws, market standoff agreements entered into by our stockholders with us or lock-up agreements entered into by our stockholders with the underwriters; however, subject to applicable securities law restrictions and excluding shares of restricted stock that will remain unvested, these shares will be able to be sold in the public market beginning 180 days after the date of this prospectus. The representatives may, in their sole discretion, release all or some portion of the shares subject to lock-up agreements at any time and for any reason. In addition, 505,731 shares of unvested restricted stock were issued and outstanding as of September 30, 2017 will become available for sale immediately upon the vesting of such shares, as applicable, and the expiration of any applicable market standoff or lock-up agreements. Shares issued upon the exercise of stock options outstanding under our equity incentive plans or pursuant to future awards granted under those plans will become available for sale in the public market to the extent permitted by the provisions of applicable vesting schedules, any applicable market standoff and lock-up agreements, and Rule 144 and Rule 701 under the Securities Act of 1933, as amended, or the Securities Act. See the section titled “Shares Eligible for Future Sale” for additional information.

Moreover, after this offering, holders of an aggregate of 64,913,502 shares of our common stock will have rights, subject to conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. We also plan to register all shares of common stock that we may issue under our equity compensation plans. Once we register these shares, they can be freely sold in the public market upon issuance and once vested, subject to volume limitations applicable to affiliates and the lock-up agreements described in the section titled “Underwriting” in this prospectus. If any of these additional shares are sold, or if it is perceived that they will be sold, in the public market, the market price of our common stock could decline.

You will incur immediate and substantial dilution as a result of this offering.

If you purchase common stock in this offering, you will incur immediate and substantial dilution of $12.86 per share, representing the difference between the initial public offering price of $18.00 per share, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, and our pro forma net tangible book value per share after giving effect to this offering and the automatic conversion of all outstanding shares of our convertible preferred stock upon the closing of this offering. As of September 30, 2017, there were 6,179,687 shares subject to outstanding options with a weighted-average exercise price of $3.06 per share. To the extent that these outstanding options are ultimately exercised or the underwriters exercise their option to purchase additional shares, you will incur further dilution. See the section titled “Dilution” for a further description of the dilution you will experience immediately after this offering.

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.

Insiders will continue to have substantial influence over us after this offering, which could limit your ability to affect the outcome of key transactions, including a change of control.

After this offering, our directors, executive officers, holders of more than 5% of our outstanding stock and their respective affiliates will beneficially own shares representing approximately 66.6% of our outstanding common stock. As a result, these stockholders, if they act together, will be able to influence our management and affairs and 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 and might affect the market price of our common stock.

Certain of our existing stockholders, including one that beneficially owns more than 5% of our outstanding common stock, have agreed to purchase approximately 5,300,000 shares of our common stock in this offering at the initial public offering price.

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. 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. In this prospectus, we have not included all of the executive compensation related information that would be required if we were not an emerging growth company. 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, we will be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

We will incur increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives and corporate governance practices.

As a public company, and particularly after we are no longer an emerging growth company, we will 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 becoming, and our efforts to comply with the requirements of being, a public company, and our management and other personnel will need to devote a substantial amount of time towards maintaining compliance with these requirements. These requirements will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, we expect that the rules and regulations applicable to us as a public company may make it more difficult and more expensive for us to obtain director and officer liability insurance, which could make it more difficult for us to attract and retain qualified members of our board of directors. 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 will be 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.

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 broad discretion in the use of the net proceeds from this offering and may not use them effectively.

We cannot specify with certainty the particular uses of the net proceeds we will receive from this offering. Our management will have broad discretion in the application of the net proceeds, including for any of the purposes described in the section titled “Use of Proceeds” in this prospectus. Our management may spend a portion or all of the net proceeds from this offering in ways that our stockholders may not desire or that may not yield a favorable return. The failure by our management to apply these funds effectively could harm our business, financial condition, results of operations and prospects. Pending their use, we may invest the net proceeds from this offering in a manner that does not produce income or that loses value.

We do not expect to pay any dividends for the foreseeable future. Investors in this offering may never obtain a return on their investment.

You should not rely on an investment in our common stock to provide dividend income. We do not anticipate that we will pay any dividends to holders of our common stock in the foreseeable future. Instead, we plan to retain any earnings to maintain and expand our existing operations. In addition, any future credit facility may contain terms prohibiting or limiting the amount of dividends that may be declared or paid on our common stock. Accordingly, investors must rely on sales of their common stock after price appreciation, which may never occur, as the only way to realize any return on their investment. As a result, investors seeking cash dividends should not purchase our common stock.

Delaware law and provisions in our amended and restated certificate of incorporation and bylaws that will become effective upon the closing of this offering 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 bylaws that will become effective upon the closing of this offering 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 will:

- 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 issues 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.

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 that will become effective upon the closing of this offering 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 that will become effective upon the closing of this offering 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.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus contains forward-looking statements. All statements other than statements of historical facts contained in this prospectus, including statements regarding our future results of operations and financial position, business strategy, product candidates, planned preclinical studies and clinical trials, research and development costs, regulatory approvals, timing and likelihood of success, as well as plans and objectives of management for future operations, are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that are in some cases beyond our control and 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.

In some cases, you can identify forward-looking statements by terms such as “may,” “will,” “should,” “would,” “expect,” “plan,” “anticipate,” “could,” “intend,” “target,” “project,” “contemplate,” “believe,” “estimate,” “predict,” “potential” or “continue” or the negative of these terms or other similar expressions. Forward-looking statements contained in this prospectus include, but are not limited to, statements about:

- the success, cost and timing of our development activities, preclinical studies and clinical trials, and in particular the development of our BBB platform technology, core programs and biomarkers;
- the extent to which any dosing limitations that we are subject to may affect the success of our product candidates;
- the impact of pre-clinical 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 of strategic collaboration agreements 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 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 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;
- 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;
- the pricing and reimbursement of our product candidates, if approved;
- 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 financial performance;
- our expectations regarding the period during which we qualify as an emerging growth company under the JOBS Act; and
- our anticipated use of the proceeds from this offering.

We have based these forward-looking statements largely on our current expectations and projections about our business, the industry in which we operate, and financial trends that we believe may affect our business, financial condition, results of operations and prospects, and these forward-looking statements are not guarantees of future performance or development. These forward-looking statements speak only as of the date of this prospectus and are subject to a number of risks, uncertainties and assumptions described in the section titled “Risk Factors” and elsewhere in this prospectus. Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified, you should not rely on these forward-looking statements as predictions of future events. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein until after we distribute this prospectus, whether as a result of any new information, future events or otherwise.

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

MARKET, INDUSTRY AND OTHER DATA

This prospectus contains estimates, projections and other information concerning our industry, our business and the markets for our product candidates. We obtained the industry, market and similar data set forth in this prospectus from our own internal estimates and research and from academic and industry research, publications, surveys and studies conducted by third parties, including governmental agencies. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances that are assumed in this information. While we believe that the data we use from third parties are reliable, we have not separately verified these data. Further, while we believe our internal research is reliable, such research has not been verified by any third party. You are cautioned not to give undue weight to any such information, projections and estimates.

In some cases, we do not expressly refer to the sources from which data is derived. In that regard, when we refer to one or more sources of this type of data in any paragraph, you should assume that other data of this type appearing in the same paragraph is derived from the same sources, unless otherwise expressly stated or the context otherwise requires.

The sources of industry and market data contained in this prospectus are listed below:

(1) *Science*, “RIPK1 Mediates Axonal Degeneration by Promoting Inflammation and Necroptosis in ALS,” Volume 353, Issue 6299, August 5, 2016

(2) The Alzheimer’s Association, “2017 Alzheimer’s Disease Facts and Figures”

(3) The Alzheimer’s Association, “Fact Sheet,” March 2017

(4) The National MPS Society, “MPS II”

(5) The Parkinson’s Disease Foundation, “Statistics on Parkinson’s”

(6) The ALS Association, “Facts You Should Know”

(7) The Michael J. Fox Foundation for Parkinson’s Research, “LRRK2 Kinase Inhibitors of Different Structural Classes Induce Abnormal Accumulation of Lamellar Bodies in Type II Pneumocytes in Non-Human Primates but are Reversible and Without Pulmonary Functional Consequences”

(8) The World Health Organization, “Dementia Fact Sheet,” May 2017

USE OF PROCEEDS

We estimate that the net proceeds from our issuance and sale of 13,888,888 shares of our common stock in this offering will be approximately $229.0 million, based on the initial public offering price of $18.00 per share, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us. If the underwriters exercise their option to purchase additional shares in full, we estimate that our net proceeds will be approximately $263.9 million.

The principal purposes of this offering are to obtain additional capital to support our operations, establish a public market for our common stock and facilitate our future access to the public capital markets. We currently anticipate that we will use the net proceeds from this offering, together with our existing resources, through 2019 as follows:

- approximately $20 to $25 million to fund the costs of Phase 1 trials in healthy volunteers for each of DNL201 and DNL151 and a Phase 1b study in LRRK2 mutation-carrying Parkinson's disease patients, as well as preparation for a potential future Phase 2 clinical trial;
- approximately $30 to $35 million to fund the costs to advance our RIPK1 program through Phase 1 and early Phase 2 clinical development, substantially represented by the planned Phase 1 clinical trial in healthy volunteers, including a cohort in Alzheimer's disease patients, for DNL747 and a Phase 2a clinical trial in ALS patients and a Phase 2a clinical trial in Alzheimer's disease patients;
- approximately $45 to $50 million to optimize and broaden our ATV and ETV platform technologies and to advance our four core antibody and enzyme replacement programs through preclinical development and IND-enabling activities;
- if we exercise our option to acquire all outstanding shares of F-star Gamma, in the aggregate, approximately $18.0 million to $50.0 million to fund the initial exercise payments; and
- the remainder to fund seed programs, general research and development activities, working capital and other general corporate activities.

We believe opportunities may exist from time to time to expand our current business through license or acquisitions of, or investments in, complementary businesses, products or technologies. While we currently have no agreements or commitments to complete any such transaction at this time, we may use a portion of the net proceeds for these purposes.

The net proceeds from this offering, together with our cash, cash equivalents and marketable securities, will not be sufficient for us to fund any of our product candidates through regulatory approval, and we will need to raise additional capital to complete the development and commercialization of our product candidates. We expect to finance our incremental cash needs through a combination of equity offerings, debt financings and potential licenses and collaboration agreements. This expected use of net proceeds from this offering represents our intentions based upon our current plans and business conditions, which could change in the future as our plans and business conditions evolve. The amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development, the status of and results from clinical trials, as well as any collaborations that we may enter into with third parties for our programs, and any unforeseen cash needs. As a result, our management will retain broad discretion over the allocation of the net proceeds. We cannot specify with certainty all of the particular uses for the net proceeds to be received upon the closing of this offering.

Pending use of the proceeds as described above, we intend to invest the proceeds in a variety of capital preservation investments, including interest-bearing, investment-grade instruments and U.S. government securities.

DIVIDEND POLICY

We have not declared or paid any cash dividends on our capital stock since our inception. We intend to retain future earnings, if any, to finance the operation and expansion of our business and do not anticipate paying any cash dividends in the foreseeable future. Payment of future cash dividends, if any, will be at the discretion of our board of directors after taking into account various factors, including our financial condition, operating results, current and anticipated cash needs, the requirements and contractual restrictions of then-existing debt instruments and other factors that our board of directors deems relevant.

CAPITALIZATION

The following table sets forth our cash, cash equivalents and marketable securities and capitalization as of September 30, 2017, as follows:

- on an actual basis;
- on a pro forma basis to reflect (1) the conversion of all outstanding shares of our convertible preferred stock into an aggregate of 60,365,020 shares of common stock upon the closing of this offering (this includes the impact to assets and stockholders' equity of those additional shares issuable upon conversion of our Series B-2 convertible preferred stock) and (2) the filing and effectiveness of our amended and restated certificate of incorporation, which will occur immediately prior to the closing of this offering, as if such conversion had occurred on September 30, 2017; and
- on a pro forma as adjusted basis to further reflect our issuance and sale of 13,888,888 shares of common stock in this offering at the initial public offering price of $18.00 per share, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

You should read this information in conjunction with our consolidated financial statements and the related notes and the sections titled "Selected Consolidated Financial Data" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" that are included elsewhere in this prospectus.

	As of September 30, 2017		
	Actual	Pro Forma	Pro Forma As Adjusted
	(in thousands, except share and per share amounts)		
Cash, cash equivalents and marketable securities	$ 190,776	$ 220,676	$ 449,676
Convertible preferred stock, par value $0.01 per share; 63,288,466 shares authorized, 58,600,315 shares issued and outstanding, actual; no shares authorized, issued or outstanding, pro forma and pro forma as adjusted	$ 348,673	$ —	$ —
Stockholder's equity (deficit):			
Preferred stock, par value $0.01 per share; no shares authorized, issued and outstanding, actual; 40,000,000 shares authorized, no shares issued and outstanding, pro forma and pro forma as adjusted	—	—	—
Common stock, par value $0.01 per share; 83,587,362 shares authorized, 13,725,567 shares issued and outstanding, actual; 400,000,000 shares authorized, 74,090,587 shares issued and outstanding, pro forma; 400,000,000 shares authorized, 87,979,475 shares issued and outstanding, pro forma as adjusted	424	1,028	1,167
Additional paid-in capital	13,087	391,056	619,917
Accumulated other comprehensive loss	(237)	(237)	(237)
Accumulated deficit	(168,810)	(168,810)	(168,810)
Total stockholders' equity (deficit)	(155,536)	223,037	452,037
Total capitalization	$ 193,137	$ 223,037	$ 452,037

The number of shares of common stock that will be outstanding after this offering is based on 74,090,587 shares of common stock outstanding as of September 30, 2017 (including our convertible preferred stock on an as-converted basis, as well as 1,764,705 shares of our Series B-2 convertible preferred stock issued after September 30, 2017), and excludes the following:

- 6,179,687 shares of common stock issuable upon exercise of options to purchase shares of our common stock outstanding as of September 30, 2017, at a weighted-average exercise price of $3.06 per share;
- 194,000 shares of common stock issuable upon exercise of options to purchase shares of our common stock that were granted after September 30, 2017, at a weighted-average exercise price of $11.64 per share;
- 81,164 shares of common stock to be issued in connection with our acquisition of Incro Pharmaceuticals;
- 7,379,238 shares of common stock reserved for future issuance under our stock-based compensation plans, consisting of:
    - 169,238 shares of common stock reserved for future issuance under our 2015 Stock Incentive Plan, or 2015 Plan, which shares will be added to the shares to be reserved under our 2017 Equity Incentive Plan, or 2017 Plan;
    - 6,210,000 shares of common stock reserved for future issuance under our 2017 Plan (excluding the 169,238 shares to be transferred from our 2015 Plan), which became effective in connection with this offering, and any additional shares that become available under our 2017 Plan pursuant to provisions thereof that automatically increase the share reserve under the plan each year, as more fully described in the section titled “Executive Compensation—Employee Benefit and Stock Plans;” and
    - 1,000,000 shares of common stock reserved for future issuance under our 2017 Employee Stock Purchase Plan, or ESPP, which became effective in connection with this offering, and any additional shares that become available under our ESPP pursuant to provisions thereof that automatically increase the share reserve under the plan each year, as more fully described in the section titled “Executive Compensation—Employee Benefit and Stock Plans.”

DILUTION

If you invest in our common stock in this offering, your ownership interest will be diluted immediately to the extent of the difference between the initial public offering price per share of our common stock and the pro forma as adjusted net tangible book value per share of our common stock immediately after this offering.

Our historical net tangible book value (deficit) as of September 30, 2017 was $(155.5) million, or $(11.33) per share of our common stock. Our historical net tangible book value (deficit) is the amount of our total tangible assets less our total liabilities and convertible preferred stock, which is not included within our stockholders' equity (deficit). Historical net tangible book value per share represents historical net tangible book value (deficit) divided by the number of shares of our common stock outstanding as of September 30, 2017.

Our pro forma net tangible book value as of September 30, 2017 was $223.0 million, or $3.01 per share of our common stock. Pro forma net tangible book value represents the amount of our total tangible assets less our total liabilities, after giving effect to the conversion of all outstanding shares of our convertible preferred stock into an aggregate of 60,365,020 shares of common stock upon the completion of this offering. This includes the impact to assets and stockholders' equity of 1,764,705 shares issuable upon conversion of our Series B-2 convertible preferred stock. Pro forma net tangible book value per share represents pro forma net tangible book value divided by the total number of shares outstanding as of September 30, 2017, after giving effect to the conversion of all outstanding shares of our convertible preferred stock into an aggregate of 60,365,020 shares of our common stock upon the completion of this offering (including 1,764,705 shares issuable upon conversion of our Series B-2 convertible preferred stock).

After giving further effect to our sale of 13,888,888 shares of common stock in this offering at the initial public offering price of $18.00 per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us, our pro forma as adjusted net tangible book value as of September 30, 2017 would have been approximately $452.0 million, or approximately $5.14 per share. This represents an immediate increase in pro forma as adjusted net tangible book value per share of $2.13 to our existing stockholders and an immediate dilution in pro forma as adjusted net tangible book value per share of approximately $12.86 to new investors purchasing common stock in this offering. Dilution per share to new investors purchasing common stock in this offering is determined by subtracting pro forma as adjusted net tangible book value per share after this offering from the initial public offering price per share paid by new investors.

The following table illustrates this dilution on a per share basis:

Initial public offering price per share		$18.00
Historical net tangible book value (deficit) per share as of September 30, 2017	$(11.33)	
Pro forma increase in net tangible book value (deficit) per share as of September 30, 2017	$ 14.34	
Pro forma net tangible book value per share as of September 30, 2017	$ 3.01	
Increase in pro forma as adjusted net tangible book value per share attributable to new investors purchasing shares in this offering	$ 2.13	
Pro forma as adjusted net tangible book value per share after this offering		$ 5.14
Dilution per share to new investors purchasing shares in this offering		$12.86

If the underwriters exercise their option to purchase 2,083,333 additional shares of common stock in this offering in full at the initial public offering price of $18.00 per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us, the pro forma as adjusted net tangible book value per share after this offering would be $5.41 per share, and the dilution in pro forma as adjusted net tangible book value per share to new investors purchasing common stock in this offering would be $12.59 per share.

The following table summarizes, on a pro forma as adjusted basis, as of September 30, 2017, the number of shares of common stock purchased from us on an as converted to common stock basis (including 1,764,705 shares issuable upon conversion of our Series B-2 convertible preferred stock), the total consideration paid, or to be paid, and the weighted-average price per share paid, or to be paid, by existing stockholders and by new investors in this offering at the initial public offering price of $18.00 per share, before deducting underwriting discounts and commissions and estimated offering expenses payable by us.

	Shares Purchased		Total Consideration		Weighted Average Price Per Share
	Number	Percent	Amount	Percent	
Existing stockholders before this offering	74,090,587	84%	$381,051	60%	$ 5.14
Investors participating in this offering	13,888,888	16	250,000	40	18.00
Total	87,979,475	100%	$631,051	100%	

The table above assumes no exercise of the underwriters' option to purchase 2,083,333 additional shares in this offering. If the underwriters' option to purchase additional shares is exercised in full, the number of shares of our common stock held by existing stockholders would be reduced to 82% of the total number of shares of our common stock outstanding after this offering, and the number of shares of common stock held by new investors participating in the offering would be increased to 18% of the total number of shares outstanding after this offering.

The number of shares of common stock that will be outstanding after this offering is based on 74,090,587 shares of common stock outstanding as of September 30, 2017 (including convertible preferred stock on an as-converted basis, as well as 1,764,705 shares of our Series B-2 convertible preferred stock issued after September 30, 2017), and excludes the following:

- 6,179,687 shares of common stock issuable upon exercise of options to purchase shares of our common stock outstanding as of September 30, 2017, at a weighted-average exercise price of $3.06 per share;
- 194,000 shares of common stock issuable upon exercise of options to purchase shares of our common stock that were granted after September 30, 2017, at a weighted-average exercise price of $11.64 per share;
- 81,164 shares of common stock to be issued in connection with our acquisition of Incro Pharmaceuticals;
- 7,379,238 shares of common stock reserved for future issuance under our stock-based compensation plans, consisting of:
    - 169,238 shares of common stock reserved for future issuance under our 2015 Plan, which shares will be added to the shares to be reserved under our 2017 Plan;
    - 6,210,000 shares of common stock reserved for future issuance under our 2017 Plan (excluding the 169,238 shares to be transferred from our 2015 Plan), which became effective in connection with this offering, and any additional shares that become available

under our 2017 Plan pursuant to provisions thereof that automatically increase the share reserve under the plan each year, as more fully described in the section titled “Executive Compensation—Employee Benefit and Stock Plans;” and

- 1,000,000 shares of common stock reserved for future issuance under our ESPP, which became effective in connection with this offering, and any additional shares that become available under our ESPP pursuant to provisions thereof that automatically increase the share reserve under the plan each year, as more fully described in the section titled “Executive Compensation—Employee Benefit and Stock Plans.”

Certain of our existing stockholders, including one that beneficially owns more than 5% of our outstanding common stock, have agreed to purchase approximately 5,300,000 shares of our common stock in this offering at the initial public offering price. The foregoing discussion does not reflect the potential purchase of any shares in this offering by these existing stockholders.

To the extent that any outstanding options are exercised or new options are issued under the equity benefit plans, or we issue additional shares of common stock or convertible securities in the future, there will be further dilution to investors participating in this offering.

SELECTED CONSOLIDATED FINANCIAL DATA

The following tables summarize our selected consolidated financial data for the periods and as of the dates indicated. We have derived our selected consolidated statements of operations and comprehensive loss data for the years ended December 31, 2015 and 2016, and the consolidated balance sheets data as of December 31, 2015 and 2016, from our audited consolidated financial statements and related notes included elsewhere in this prospectus. We have derived the selected consolidated statements of operations and comprehensive loss data for the nine months ended September 30, 2016 and 2017, and the consolidated balance sheet data as of September 30, 2017, from our unaudited interim condensed consolidated financial statements and related notes included elsewhere in this prospectus. The unaudited interim condensed consolidated financial statements have been prepared on the same basis as the audited consolidated financial statements and reflect, in the opinion of management, all adjustments, which include only normal, recurring adjustments that are necessary to present fairly the unaudited interim condensed consolidated financial statements. Our historical results are not necessarily indicative of the results that may be expected in the future, and the results for the nine months ended September 30, 2017, are not necessarily indicative of results to be expected for the full year or any other period. You should read the consolidated financial and other data below in conjunction with the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our consolidated financial statements and related notes included elsewhere in this prospectus.

	Year Ended December 31,		Nine Months Ended September 30,	
	2015	2016	2016	2017
	(in thousands, except share and per share amounts)			
Consolidated Statements of Operations and Comprehensive Loss Data:				
Operating expenses:				
Research and development	$ 11,571	$ 75,702	$ 58,972	$ 55,989
General and administrative	5,108	11,731	8,685	10,611
Total operating expenses	16,679	87,433	67,657	66,600
Loss from operations	(16,679)	(87,433)	(67,657)	(66,600)
Interest income (expense), net	(109)	781	359	1,302
Net loss	(16,788)	(86,652)	(67,298)	(65,298)
Other comprehensive income (loss)	—	(373)	(131)	136
Comprehensive loss	$ (16,788)	$ (87,025)	$ (67,429)	$ (65,162)
Net loss per share, basic and diluted (1)	$ (5.58)	$ (13.49)	$ (11.43)	$ (6.77)
Weighted average number of shares outstanding, basic and diluted (1)	3,006,379	6,424,720	5,888,385	9,643,686
Pro forma net loss per share, basic and diluted (unaudited) (1)		$ (1.77)		$ (0.96)
Pro forma weighted-average common shares outstanding, basic and diluted (unaudited) (1)		48,924,244		68,244,028

(1) See the consolidated statements of operations and Note 12 to our consolidated financial statements, and the condensed consolidated statements of operations and Note 9 to our unaudited condensed consolidated financial statements, for further details on the calculation of net

loss per share, basic and diluted, and the weighted-average number of shares used in the computation of the per share amounts and unaudited pro forma information.

	As of December 31,		As of September 30,
	2015	2016	2017
	(in thousands)		
Consolidated Balance Sheets Data:			
Cash, cash equivalents and marketable securities	$ 30,740	$ 250,911	$ 190,776
Working capital (1)	29,950	172,849	178,089
Total assets	36,683	271,067	210,309
Total liabilities	4,009	16,548	17,172
Convertible preferred stock	48,308	348,673	348,673
Accumulated deficit	(16,860)	(103,512)	(168,810)
Total stockholders' deficit	(15,634)	(94,154)	(155,536)

(1) We define working capital as current assets less current liabilities. See our consolidated financial statements and condensed consolidated financial statements for further details regarding our current assets and current liabilities.

MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

You should read the following discussion and analysis of our financial condition and results of operations together with the section titled "Selected Consolidated Financial Data" and our consolidated financial statements and the related notes to those statements included elsewhere in this prospectus. This discussion and analysis and other parts of this prospectus contain forward-looking statements based upon current beliefs, plans and expectations related to future events and our future financial performance that involve risks, uncertainties and assumptions, such as statements regarding our intentions, plans, objectives, expectations, forecasts and projections. Our actual results and the timing of selected events could differ materially from those anticipated in these forward-looking statements as a result of several factors, including those set forth under the section titled "Risk Factors" and elsewhere in this prospectus. You should carefully read the "Risk Factors" to gain an understanding of the important factors that could cause actual results to differ materially from our forward-looking statements. Please also see the section titled "Special Note Regarding Forward-Looking Statements."

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 total portfolio currently consists of eleven programs. To prioritize the allocation of our resources, we designate certain programs as core programs and others as seed programs, and we currently have six core programs and five seed programs. Our core programs are at various stages of clinical and preclinical development. Our most advanced core programs are our LRRK2 inhibitor program to address Parkinson's disease and our RIPK1 inhibitor program to address Alzheimer's disease and 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. DNL201 is currently in a Phase 1 clinical trial in healthy volunteers in the United States. DNL151 has completed IND-enabling preclinical studies. We submitted a CTA for DNL151 to the Netherlands Health Authority in October 2017 and it was accepted in November 2017. 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. DNL747 is in IND-enabling preclinical studies and we plan to submit a CTA in early 2018.

We have also developed proprietary drug delivery platform technology designed to deliver large molecules across the BBB. We are currently optimizing and broadening this platform technology. Our ATV and ETV platforms are modular BBB delivery technologies for large molecule therapeutics, including antibodies, enzyme and other proteins. We plan to have multiple product candidates that utilize our ATV or ETV platforms enter clinical development in 2019 and 2020, including molecules targeting aSyn, IDS, TREM2, BACE1 and Tau.

To complement our internal capabilities, we have entered into arrangements with biopharmaceutical companies, patient-focused data 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. Key operational and financing milestones include:

- In May 2015, we commenced operations and began assembling a team with deep scientific, clinical, business and leadership experience and expertise.
- In May 2015, we entered into a preferred stock purchase agreement, which was subsequently amended, pursuant to which we raised aggregate proceeds of $219.3 million from issuances of our Series A-1 convertible preferred stock and Series A-2 convertible preferred stock in multiple closings between May 2015 and June 2016.
- In June 2015, in order to acquire certain patent rights and a product candidate, we acquired Incro Pharmaceuticals, or Incro, for $1.5 million, which consisted of $0.9 million in assumed liabilities and $0.6 million in shares of our common stock. In September 2016, following the satisfaction of certain milestones, we issued an additional $5.3 million in shares of common stock in connection with this acquisition.
- In June 2016, we entered into an exclusive license agreement with Genentech for the rights to certain patents, other intellectual property and a product candidate to expand and further progress our LRRK2 program.
- In June 2016, we amended our preferred stock purchase agreement, pursuant to which we raised an additional $130.0 million in proceeds from issuances of our Series B-1 convertible preferred stock in multiple closings between June 2016 and August 2016.
- In August 2016, we entered into a license and collaboration agreement with F-star. The goal of the collaboration is the development of certain constant Fc domains of an antibody with non-native antigen binding activity, or Fcabs, to enhance delivery of therapeutics across the BBB into the brain. In connection with the entry into the license and collaboration agreement, we purchased an option to acquire all outstanding shares of F-star Gamma pursuant to a pre-negotiated buy-out option agreement.
- In April 2017, we filed an IND with the FDA for our most advanced therapeutic product candidate, DNL201, and we initiated a Phase 1 clinical trial of DNL201 in healthy volunteers in the United States in June 2017.
- In November 2017, we further amended our preferred stock purchase agreement, pursuant to which we raised an additional $30.0 million in gross proceeds from issuances of our Series B-2 convertible preferred stock in multiple closings.

We do not have any products approved for sale and have not generated any product revenue since our inception. To date, we have funded our operations primarily with proceeds from the sale and issuance of convertible preferred stock. From our inception through September 30, 2017, we have raised aggregate cash proceeds of $349.3 million from the issuance of our convertible preferred stock.

We have incurred significant operating losses to date and expect to continue to incur operating losses for the foreseeable future. Our ability to generate product revenue will depend on the successful

development and eventual commercialization of one or more of our product candidates. Our net losses were $86.7 million and $16.8 million for the years ended December 31, 2016 and 2015, respectively, and $65.3 million for the nine months ended September 30, 2017. As of September 30, 2017, we had an accumulated deficit of $168.8 million. We expect to continue to incur significant expenses and operating losses as we advance our LRRK2 and RIPK1 programs through preclinical and 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. In addition, upon the completion of this offering we expect to incur additional costs associated with operating as a public company.

License and Collaboration Agreements

F-star

On August 24, 2016, we entered into a License and Collaboration Agreement, or the Collaboration Agreement, with F-star. The goal of the collaboration is the development of Fcabs to enhance delivery of therapeutics across the BBB into the brain. The collaboration leverages F-star's modular antibody technology and our expertise in the development of therapies for neurodegenerative diseases.

Under the terms of the Collaboration Agreement, we can nominate up to three Fcab targets, or Accepted Fcab Targets, within the first three years of the date of the Collaboration Agreement; and we have selected TfR as the first Accepted Fcab Target. With respect to each Accepted Fcab Target, we can nominate up to eight Fab targets, or Accepted Fab Targets, which are targets bound by the variable domains of an antibody or other therapeutic modalities, or Fabs. Under the terms of the Collaboration Agreement, we paid F-star Gamma an upfront fee of $5.5 million, which includes selection of the first Accepted Fcab Target under the Collaboration Agreement. We are obligated to pay a one-time fixed fee in the low single-digit millions for each additional Accepted Fcab Target we select, technical milestone payments for each Accepted Fcab Target, up to a maximum of $15.0 million in the aggregate for all Accepted Fcab Targets, and, at specified times, monthly exclusivity fees for Accepted Fcab Targets and Accepted Fab Targets, which may be eliminated in certain circumstances. We are also responsible for certain research costs incurred by F-star 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.

In connection with the entry into the Collaboration Agreement, we also purchased an option for an upfront option fee of $0.5 million, or the buy-out option, to acquire all of the outstanding shares of F-star Gamma pursuant to a pre-negotiated buy-out option agreement, or the Option Agreement. If we exercise this buy-out option, we will be required to make initial exercise payments ranging from, in the aggregate, approximately $18.0 million to $50.0 million, plus a payment for the estimated net cash held by F-star Gamma at the time of such exercise. In addition to these initial exercise payments, we would be required to make certain contingent payments upon the achievement of certain preclinical, clinical, regulatory and commercial milestones, up to a maximum amount of $447.0 million in the aggregate. The amount of the initial exercise and contingent payments varies based on whether F-star delivers an Fcab that meets pre-defined criteria, whether the Fcab has been identified solely by us or solely by F-star or jointly by us and F-star and the timing of our exercise of the buy-out option. Following exercise of the buy-out option, we will not be required to make any further milestone or royalty payments under the Collaboration Agreement.

We recognized the entire $5.5 million upfront fee in research and development expense for the year ended December 31, 2016. We recognized an additional $0.3 million of research and development expense related to the funding of F-star Gamma research costs during the year ended December 31, 2016.

Genentech

On June 17, 2016, we entered into an Exclusive License Agreement with Genentech. The agreement gives us access to Genentech's preclinical stage LRRK2 small molecule program, which can be used to enhance and further progress our in-house LRRK2 program for Parkinson's disease. As consideration, we paid an upfront fee of $8.5 million and a technology transfer fee of $1.5 million, both of which are included in research and development expense for the year ended December 31, 2016 as there is no alternative future use of the rights acquired in other research and development projects.

We 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 us, (ii) the date a compound was first discovered, derived or optimized by us, (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. We also have 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 first clinical milestone of $2.5 million became due upon first patient dosing in the Phase 1 clinical trial for DNL201. The full amount was recognized in research and development expense in the nine months ended September 30, 2017.

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

Components of Operating Results

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 CROs, preclinical testing 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
- 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 study.

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.

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 when operating as a public company and as we advance our product candidates through clinical development, which will also likely require us to increase our general and administrative expenses.

Interest Income (Expense), Net

Interest income (expense), net, consists primarily of interest income and investment income earned on our cash, cash equivalents and marketable securities.

Results of Operations

Comparison of the Nine Months Ended September 30, 2016 and 2017

The following table sets forth the significant components of our results of operations (in thousands):

	Nine Months Ended September 30,		
	2016	2017	Change
Operating expenses:			
Research and development	$ 58,972	$ 55,989	$(2,983)
General and administrative	8,685	10,611	1,926
Total operating expenses	67,657	66,600	(1,057)
Loss from operations	(67,657)	(66,600)	1,057
Interest income, net	359	1,302	943
Net loss	$(67,298)	$(65,298)	$ 2,000

Research and development expenses. Research and development expenses were $59.0 million for the nine months ended September 30, 2016 compared to $56.0 million for the nine months ended September 30, 2017.

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

	Nine Months Ended September 30,		
	2016	2017	Change
LRRK2 program external expenses (1)	$14,458	$11,803	$(2,655)
RIPK1 program external expenses (2)	15,611	7,379	(8,232)
BBB platform external expenses (3)	7,292	2,655	(4,637)
Other external research and development expenses	5,308	7,663	2,355
Personnel related expenses (4)	10,479	16,713	6,234
Other unallocated research and development expenses	5,824	9,776	3,952
Total research and development expenses	$58,972	$55,989	$(2,983)

(1) Payments under the license agreement with Genentech for an upfront payment and technology transfer fee totaling $10.0 million and a milestone payment of $2.5 million are included in the amounts for the nine months ended September 30, 2016 and 2017, respectively.
(2) The amount for the nine months ended September 30, 2016 includes $5.3 million in expenses related to contingent stock consideration issued in connection with our acquisition of Incro.
(3) The amount for the nine months ended September 30, 2016 includes $5.5 million in expenses related to a payment made under our license and collaboration agreement with F-star.
(4) Personnel related expenses include stock-based compensation expense of $1.6 million for the nine months ended September 30, 2016 and $1.9 million for the nine months ended September 30, 2017, reflecting an increase of $0.3 million.

The decrease in total research and development expenses of $3.0 million was primarily attributable to an $8.2 million decrease in RIPK1 program external expenses and a $4.6 million decrease in BBB platform external expenses. The decrease in RIPK1 is primarily due to the $5.3 million in upfront expenses incurred in the nine months ended September 30, 2016 related to contingent consideration in connection with our acquisition of Incro, and the termination of the clinical trial for DNL104 in April 2017. The decrease in BBB platform expenses is due to the payment of $5.5 million made under our license and collaboration agreement with F-star in the nine months ended September 30, 2016.

These decreases were partially offset by a $6.2 million increase in personnel related expenses due to an increase in our research and development headcount and a $4.0 million increase in other unallocated research and development expenses. The increase in other unallocated research and development expenses consisted of an increase in lab consumable expenses of $1.9 million and an increase in facilities related expenses of $2.1 million, attributable to increases in research and development headcount and the move to our new headquarters in August 2016 which allowed us to significantly increase our lab space capacity.

General and administrative expenses. General and administrative expenses were $8.7 million for the nine months ended September 30, 2016 compared to $10.6 million for the nine months ended September 30, 2017. The increase of $1.9 million was primarily attributable to a $0.8 million increase in patent expenses and professional services to support our ongoing operations and $0.2 million related to increased facilities expenses attributable to general and administrative expenses resulting from the move to our new headquarters in August 2016.

Interest income, net. Interest income, net was $0.4 million for the nine months ended September 30, 2016 compared to $1.3 million for the nine months ended September 30, 2017. We began investing our excess cash in marketable securities in June 2016. As such, the increase of $0.9 million reflects that the nine months ended September 30, 2016 includes less than four months of income from marketable securities, compared to the nine months ended September 30, 2017, which includes nine months of income from marketable securities.

Comparison of the Years Ended December 31, 2015 and 2016

The following table sets forth the significant components of our results of operations (in thousands):

	Year Ended December 31,		
	2015	2016	Change
Operating expenses:			
Research and development	$ 11,571	$ 75,702	$ 64,131
General and administrative	5,108	11,731	6,623
Total operating expenses	16,679	87,433	70,754
Loss from operations	(16,679)	(87,433)	(70,754)
Interest income (expense), net	(109)	781	890
Net loss	$(16,788)	$(86,652)	$(69,864)

Research and development expenses. Research and development expenses were $11.6 million for the year ended December 31, 2015 compared to $75.7 million for the year ended December 31, 2016.

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

	Year Ended December 31,		
	2015	2016	Change
LRRK2 program external expenses (1)	$ 777	$ 16,770	$ 15,993
RIPK1 program external expenses (2)	2,256	19,106	16,850
BBB platform external expenses (3)	33	8,016	7,983
Other external research and development expenses	3,305	8,020	4,715
Personnel related expenses (4)	2,943	14,974	12,031
Other unallocated research and development expenses	2,257	8,816	6,559
Total research and development expenses	$ 11,571	$ 75,702	$ 64,131

(1) The amount for the year ended December 31, 2016 includes an upfront payment and technology transfer license payment to Genentech totaling $10.0 million.
(2) The amount for the years ended December 31, 2015 and 2016 include $1.5 million and $5.3 million in expenses related to initial and contingent stock consideration, respectively, both issued in connection with our acquisition of Incro.
(3) The amount for the year ended December 31, 2016 includes $5.5 million in expenses related to a payment made under our license and collaboration agreement with F-star.
(4) Personnel related expenses include stock-based compensation expense of $0.1 million in 2015 and $2.1 million in 2016, with the increase driven by higher headcount and a higher estimated fair value of our common stock.

The increase in research and development expenses of $64.1 million is a result of several factors. The increase was attributable to a $16.9 million increase in our RIPK1 program external expenses, a $16.0 million increase in our LRRK2 program external expenses, an $8.0 million increase in our BBB platform technology external expenses and a $12.0 million increase in personnel related expenses. In addition, the increase reflects the fact that the expenses in the year ended December 31, 2015 only include seven months of operations, as we commenced operations in May 2015.

The increase in our RIPK1 program external expenses is primarily attributable to the increased fair value and number of shares of our common stock issued during 2016 to former shareholders of Incro as contingent consideration for our acquisition of Incro, as well as the expenses incurred for the preparation for and initiation of the DNL104 Phase 1 clinical trial. The increase in our LRRK2 program external expenses is primarily attributable to an upfront payment and a technology transfer license payment to Genentech totaling $10.0 million in the year ended December 31, 2016, as well as increased external research services to progress DNL201 and other LRRK2 molecules into development. The increase in our BBB platform technology external expenses is primarily attributable to the $5.5 million upfront fee payment to F-star Gamma in the year ended December 31, 2016. The increase in personnel related expenses is attributable to a $10.0 million increase in salaries and benefits and a $2.0 million increase in stock-based compensation expense, both due primarily to an increase in our research and development headcount.

Furthermore, there was a $6.6 million increase in other unallocated research and development expenses. This was primarily composed of an increase in lab consumable expenses of $3.4 million and an increase in facilities related expenses of $2.7 million. These increases are partially attributable to the fact that these expenses include seven and twelve months of expenses in the years ended December 31, 2015 and 2016, respectively, and also reflect increases in research and development headcount and increased expenses related to the move to our new headquarters in August 2016.

General and administrative expenses. General and administrative expenses were $5.1 million for the year ended December 31, 2015 compared to $11.7 million for the year ended December 31, 2016. The increase of $6.6 million was primarily attributable to a $2.8 million increase in employee salaries and benefits as we expanded our headcount, a $2.5 million increase in patent and professional services to support our ongoing operations, a $0.5 million increase in stock-based compensation expense and $0.3 million related to increased facilities related expenses resulting from the move to our new headquarters in August 2016 and reflects the fact that the expenses in the year ended December 31, 2015 include only seven months of operations, as we commenced operations in May 2015.

Interest income (expense), net. Interest expense was $(0.1) million for the year ended December 31, 2015 compared to interest income of $0.8 million for the year ended December 31, 2016. The expense for the year ended December 31, 2015 represents interest expense on a $5.0 million promissory note outstanding from January 2015 until May 2015, at which time this note, along with the accrued interest, was converted into Series A-1 convertible preferred stock. The income for the year ended December 31, 2016 represents income from marketable securities earned in the period from June 2016 to December 2016, during which we invested our excess cash in marketable securities.

Liquidity and Capital Resources

Sources of Liquidity

From our inception through September 30, 2017, we have funded our operations primarily through the sale and issuance of our convertible preferred stock. From our inception through September 30, 2017, we raised aggregate cash proceeds of $349.3 million from the issuance of our convertible preferred stock. As of September 30, 2017, we had cash, cash equivalents and marketable securities in the amount of $190.8 million.

Future Funding Requirements

To date, we have not generated any revenue. We do not expect to generate any meaningful revenue unless and until we obtain regulatory approval of and commercialize any of our product

candidates or enter into collaborative agreements with third parties, and we do not know when, or if, either will occur. We expect to continue to incur significant losses for the foreseeable future, and we expect the losses to increase as we continue the development of, and seek regulatory approvals for, our product candidates, and begin to commercialize any approved products. 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. Moreover, following the completion of this offering, we expect to incur additional costs associated with operating as a public company. We anticipate that we will need substantial additional funding in connection with our continuing operations.

Until we can generate a sufficient amount of revenue from the commercialization of our product candidates or from collaborative agreements with 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 $168.8 million through September 30, 2017. 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.

The expected use of the net proceeds from this offering represents our intentions based upon our current plans and business conditions. However, we have based these estimates on assumptions that may prove to be wrong, and we could use our capital resources sooner than we expect.

The timing and amount of our operating expenditures will depend largely on:

- 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):

	Year Ended December 31,		Nine Months Ended September 30,	
	2015	2016	2016	2017
Cash used in operating activities	$(15,052)	$ (72,359)	$ (53,993)	$(58,299)
Cash provided by (used in) investing activities	(3,062)	(219,004)	(200,057)	53,983
Cash provided by financing activities	48,854	300,476	300,480	732
Net increase (decrease) in cash and cash equivalents	$ 30,740	$ 9,113	$ 46,430	$ (3,584)

Cash Used in Operating Activities

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 charges 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.

During the nine months ended September 30, 2016, cash used in operating activities was $54.0 million, which consisted of a net loss of $67.3 million, adjusted by non-cash charges of $8.5 million and cash provided by changes in our operating assets and liabilities of $4.8 million. The non-cash charges consisted primarily of the expense recognized for the estimated fair value of our common stock issued in connection with the acquisition of Incro of $5.3 million and stock-based compensation expense of $2.3 million. The change in our operating assets and liabilities was primarily due to an increase of $3.1 million in accrued and other liabilities and an increase of $1.6 million in accounts payable.

During the year ended December 31, 2016, cash used in operating activities was $72.4 million, which consisted of a net loss of $86.7 million, adjusted by non-cash charges of $10.0 million and cash provided by changes in our operating assets and liabilities of $4.3 million. The non-cash charges consisted primarily of the expense recognized for the fair value of our common stock issued in connection with the acquisition of Incro of $5.3 million and stock-based compensation expense of $3.0 million. The change in our operating assets and liabilities was primarily due to an increase of $5.4 million of accrued and other liabilities. Our accrued liabilities increased due to employee bonuses and general business expenses, reflective of our increased headcount and expenses. This was partially

offset by an increase in restricted cash of $0.5 million associated with the lease for our new headquarters and an increase of $0.5 million in prepaid expenses and other assets mainly associated with prepayments made for ongoing research and development being conducted by third-party service providers.

During the year ended December 31, 2015, cash used in operating activities was $15.1 million, which consisted of a net loss of $16.8 million, adjusted by non-cash charges of $1.3 million and cash provided by changes in our operating assets and liabilities of $0.4 million. The non-cash charges consisted primarily of the expense recognized for the fair value of our common stock issued in connection with the acquisition of Incro of $0.6 million, and stock-based compensation expense of $0.5 million. The change in our operating assets and liabilities was primarily due to an increase of $3.3 million of accounts payable, accrued and other liabilities. Our accrued liabilities increased due to employee bonuses and general business expenses, reflective of the increased headcount and expenses. This was partially offset by an increase in prepaid expenses and other assets of $2.7 million primarily associated with prepayments made for ongoing research and development being conducted by third-party service providers and the deferral of employee bonuses.

Cash Provided by (Used in) Investing Activities

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 short-term marketable securities and $1.8 million of capital expenditures to purchase property and equipment.

During the nine months ended September 30, 2016, cash used in investing activities was $200.1 million, which primarily consisted of $195.7 million of purchases of short-term marketable securities and $3.8 million of capital expenditures to purchase property and equipment.

During the year ended December 31, 2016, cash used in investing activities was $219.0 million, which consisted of $226.4 million of purchases of marketable securities, $6.1 million of capital expenditures to purchase property and equipment and $0.5 million of purchases of intangible assets, partially offset by $14.0 million in proceeds from the maturity of marketable securities.

During the year ended December 31, 2015, cash used in investing activities was $3.1 million, all of which related to capital expenditures to purchase property and equipment.

Cash Provided by Financing Activities

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.

During the nine months ended September 30, 2016, cash provided by financing activities was $300.5 million, which primarily consisted of net proceeds from the issuances of shares of our convertible preferred stock.

During the years ended December 31, 2015 and 2016, cash provided by financing activities was $48.9 million and $300.5 million, respectively, which primarily consisted of net proceeds from the issuances of shares of our convertible preferred stock and convertible promissory note, which has since been converted to convertible preferred stock.

Since our inception through December 31, 2016, we have raised an aggregate of approximately $348.6 million in net proceeds, through the issuance of shares of our convertible preferred stock, net of

$0.7 million in issuance costs, which we have used to fund our operations. During 2016, net proceeds from our sale of Series A and Series B-1 convertible preferred stock were $300.4 million. During 2015, net proceeds from our sale of Series A-1 convertible preferred stock were $43.2 million and net proceeds from the sale and issuance of a convertible promissory note was $5.0 million.

Off-Balance Sheet Arrangements

We have not entered into any off-balance sheet arrangements. Our license and collaboration agreements with F-star represent a variable interest in a variable interest entity, or VIE, F-star Gamma. However, we do not consolidate F-star Gamma in our consolidated financial statements because we are not considered to be its primary beneficiary.

Contractual Obligations and Commitments

The following table summarizes our contractual obligations as of December 31, 2016 (in thousands):

	Total	Less Than 1 Year	1-3 Years	3-5 Years	More Than 5 Years
Operating lease obligations (1)	$21,039	$ 2,510	$5,250	$5,574	$ 7,705
Total contractual obligations	$21,039	$ 2,510	$5,250	$5,574	$ 7,705

(1) We lease our former and current facilities under operating leases. In September 2015, we entered into a lease for our current laboratory and office space that commenced in August 2016 and expires in July 2024. The minimum lease payments above do not include any related common area maintenance charges or real estate taxes.

In the normal course of business, we enter into various firm purchase commitments primarily related to research and development activities. As of December 31, 2016, we had noncancelable purchase commitments of $1.0 million and contractual obligations under license agreements of $0.2 million.

Pursuant to certain license agreements, including our agreements with Genentech and F-star, we have obligations to make future milestone and royalty payments to other parties. Additionally, we have an option to acquire all outstanding shares of F-star Gamma for initial exercise payments ranging from $18.0 million to $50.0 million in the aggregate, plus the estimated net cash held by F-star Gamma at the time of such purchase. In addition to these initial exercise payments, we would be required to make certain contingent payments up to a maximum amount of $447.0 million in the aggregate. However, we are unable to estimate the timing or likelihood of achieving the milestones or of exercising the option to purchase the outstanding shares of F-star Gamma and, therefore, any related payments are not included in the table above.

Effective September 2017, we entered into a development and manufacturing services agreement, as amended, the DMSA or the Lonza agreement, with Lonza Sales AG, or 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, 2017, we had not incurred any obligations or made any purchase commitments under the DMSA. In October 2017, we executed the first purchase order of up to $0.7 million, the activities under which will commence prior to the end of 2017.

Critical Accounting Policies and Significant Judgments and Estimates

This discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with generally accepted accounting principles in the United States, or GAAP. The preparation of these 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 consolidated financial statements, as well as the reported 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. While our significant accounting policies are described in more detail in the notes to our consolidated financial statements included elsewhere in this prospectus, we believe that the following accounting policies are critical to understanding our historical and future performance, as these policies relate to the more significant areas involving management's judgments and estimates.

Research and Development Expenses

We record research and development expenses to operations as incurred. Research and development expenses represent costs incurred by us for the discovery and development of our product candidates and the development of our BBB platform technology and include: employee-related expenses, including salaries, benefits, travel and non-cash stock-based compensation expense; external research and development expenses incurred under arrangements with third parties, such as CROs, preclinical testing organizations, CMOs, academic and non-profit institutions and consultants; costs to acquire technologies to be used in research and development that have not reached technological feasibility and have no alternative future use; license fees; and other expenses, which include direct and allocated expenses for laboratory, facilities and other costs.

As part of the process of preparing financial statements, we are required to estimate and accrue expenses. A portion of our research and development expenses are external costs, which we track on a program-specific basis once a program has commenced a late-stage IND-enabling study. We record the estimated expenses of research and development activities conducted by third-party service providers based upon the estimated amount of services provided within research and development expense in the statements of operations and comprehensive loss. These services include the conduct of preclinical studies and clinical trials, contract manufacturing activities and consulting services. If the costs have been prepaid, this expense reduces the prepaid expenses in the balance sheet, and if not yet invoiced, the costs are included in accrued liabilities in the balance sheet. These costs are a significant component of our research and development expenses. We record amortization of prepaid expenses or accrued expenses for these costs based on the estimated amount of work completed and in accordance with agreements established with these third parties.

Costs for certain research and development activities are recognized based on an evaluation of the progress to completion of specific tasks. We estimate the amount of work completed through discussions with internal personnel and external service providers as to the progress or stage of completion of the services and the agreed-upon fee to be paid for such services. We make significant judgments and estimates in determining the accrued balance in each reporting period. As actual costs become known, we adjust our accrued estimates. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed may vary from our estimates and could result in us reporting amounts that are too high or too low in any particular period. Our accrued expenses are dependent, in part, upon the receipt of timely and accurate reporting from external clinical research organizations and other third-party

service providers. To date, we have not experienced material differences between our accrued expenses and actual expenses. However, due to the nature of estimates, we cannot assure you that we will not make changes to our estimates in the future as we become aware of additional information about the status or conduct of our clinical trials and other research activities.

Variable Interest Entities

We assess whether we are the primary beneficiary of a VIE at the inception of the arrangement and at each reporting date. This assessment is based on our power to direct the activities of the VIE that most significantly impact the VIE's economic performance and our obligation to absorb losses or the right to receive benefits from the VIE that could potentially be significant to the VIE.

Stock-Based Compensation

We have granted stock-based awards, consisting of stock options and restricted stock, to our employees, certain non-employee consultants and certain members of our board of directors. We measure stock-based compensation expense for restricted stock and stock options granted to our employees and directors on the date of grant and recognize the corresponding compensation expense of those awards over the requisite service period, which is generally the vesting period of the respective award. We account for stock-based compensation arrangements with non-employee consultants using a fair value approach. The estimated fair value of unvested options granted to non-employee consultants is remeasured at each reporting date through the date of final vesting. As a result, the noncash charge to operations for nonemployee options with vesting conditions is affected in each reporting period by changes in the estimated fair value of our common stock. We adjust for actual forfeitures as they occur.

We have also granted stock options that vest in conjunction with certain performance and market conditions to certain key employees. At each reporting date, we are required to evaluate whether the achievement of the performance or market condition is probable. Compensation expense is recorded over the appropriate service period based on our assessment of accomplishing each performance or market provision or the occurrence of other events that may have caused the awards to accelerate and vest. See the section titled "Executive Compensation" for additional information.

We estimate the fair value of stock options granted to our employees and directors on the grant date, and the resulting stock-based compensation expense, using the Black-Scholes option-pricing model. The Black-Scholes option-pricing model requires the use of highly subjective assumptions which determine the fair value of stock-based awards. These assumptions include:

- *Expected Term*. Our expected term represents the period that our stock-based awards 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), as we do not have sufficient historical data to use any other method to estimate expected term.
- *Expected Volatility*. As there has been no public market for our common stock to date, and as a result we do not have any trading history of our common stock, the expected volatility is estimated based on the average volatility for comparable publicly traded biopharmaceutical companies over a period equal to the expected term of the stock option grants. The comparable companies are chosen based on their similar size, stage in the life cycle or area of specialty.
- *Risk-Free Interest Rate*. The risk-free interest rate is based on the U.S. Treasury zero coupon issues in effect at the time of grant for periods corresponding with the expected term of the stock option grants.

- *Expected Dividend*. We have never paid dividends on our common stock and have no plans to pay dividends on our common stock. Therefore, we use an expected dividend yield of zero.

For options granted to non-employee consultants, the fair value of these options is also remeasured using the Black-Scholes option-pricing model reflecting the same assumptions as applied to employee options in each of the reported periods, other than the expected life, which is assumed to be the remaining contractual life of the option.

As there has been no public market for our common stock to date, the estimated fair value of our common stock has been determined by our board of directors, with input from management, considering our most recently available third-party valuations of common stock and our board of directors' assessment of additional objective and subjective factors that it believed were relevant, and factors that may have changed from the date of the most recent valuation through the date of the grant. These factors include, but are not limited to: our most recently available valuations of our common stock by an unrelated third party; the prices at which we sold shares of our convertible preferred stock to outside investors in arms-length transactions; the rights, preferences and privileges of our convertible preferred stock relative to those of our common stock; our results of operations, financial position and capital resources; current business conditions and projections; the lack of marketability of our common stock; the hiring of key personnel and the experience of management; the risk inherent in the development of our products; our stage of development and material risks related to its business; the fact that the option grants involve illiquid securities in a private company; and the likelihood of achieving a liquidity event, such as an initial public offering or sale, in light of prevailing market conditions.

We have periodically determined the estimated fair value of our common stock at various dates using contemporaneous valuations performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants' Accounting and Valuation Guide, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation*, or the Practice Aid. The Practice Aid identifies various available methods for allocating enterprise value across classes and series of capital stock to determine the estimated fair value of common stock at each valuation date. In accordance with the Practice Aid, our board of directors considered the following methods:

- *Current Value Method.* Under the Current Value Method, or CVM, our value is determined based on our balance sheet. This value is then first allocated based on the liquidation preference associated with preferred stock issued as of the valuation date, and then any residual value is assigned to the common stock.
- *Option-Pricing Method.* Under the option-pricing method, or OPM, shares are valued by creating a series of call options with exercise prices based on the liquidation preferences and conversion terms of each equity class. The estimated fair values of the preferred and common stock are inferred by analyzing these options.
- *Probability-Weighted Expected Return Method.* The probability-weighted expected return method, or PWERM, is a scenario-based analysis that estimates value per share based on the probability-weighted present value of expected future investment returns, considering each of the possible outcomes available to us, as well as the economic and control rights of each share class.

Our common stock valuation as of May 31, 2015 was prepared using a hybrid between the CVM and OPM, the latter of which was based on the price at which we sold shares of our Series A-1 convertible preferred stock. The deemed fair value was determined by weighting these two methodologies differently resulting in an increased estimated fair value of our common stock for financial reporting purposes.

Our common stock valuations as of March 31, 2016, June 30, 2016, September 30, 2016, and December 31, 2016 were prepared using the back-solve method of OPM, which derives the implied equity value for one type of equity security from a contemporaneous transaction involving another type of security.

Our common stock valuations as of March 31, 2017, June 30, 2017 and September 30, 2017 were prepared using the hybrid method, which is a hybrid between the PWERM and OPM, consistent with how such hybrid method is described in the Practice Aid.

Our board of directors and management develop best estimates based on application of these approaches and the assumptions underlying these valuations, giving careful consideration to the advice from our third-party valuation expert. Such estimates involve inherent uncertainties and the application of significant judgment. As a result, if factors or expected outcomes change and we use significantly different assumptions or estimates, our equity-based compensation could be materially different. Following the closing of this offering, our board of directors will determine the fair market value of our common stock based on its closing price as reported on the date of grant on the primary stock exchange on which our common stock is traded.

The intrinsic value of all outstanding options as of September 30, 2017 was approximately $92.3 million, based on the initial public offering price of $18.00 per share, of which approximately $9.3 million is related to vested options and approximately $83.0 million is related to unvested options.

JOBS Act

We are an emerging growth company under the JOBS Act. As an emerging growth company, we may delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have nonetheless irrevocably elected not to avail ourselves of this exemption and, as a result, upon completion of this offering we will adopt new or revised accounting standards on the relevant dates on which adoption of such standards is required for other public companies.

We will remain an emerging growth company until the earliest of (i) the last day of our first fiscal year in which we have total annual gross revenues of $1.07 billion or more, (ii) the date on which we are deemed to be a “large accelerated filer” under the rules of the SEC with at least $700.0 million of outstanding equity securities held by non-affiliates, (iii) the date on which we have issued more than $1.0 billion in non-convertible debt securities during the previous three years, or (iv) the last day of our fiscal year following the fifth anniversary of the date of the completion of this offering.

Quantitative and Qualitative Disclosures About Market Risk

Interest Rate Sensitivity

We are exposed to market risk related to changes in interest rates. We had cash, cash equivalents and marketable securities of $190.8 million as of September 30, 2017, 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 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 the Euro, and we therefore are subject to foreign exchange risk. The fluctuation in the value of the U.S. dollar against the Euro affects the reported amounts of expenses, assets and liabilities associated with a limited number of preclinical and clinical activities. We do not currently engage in any hedging activity to reduce our potential exposure to currency fluctuations, although we may choose to do so in the future. A hypothetical 10% change in foreign exchange rates during any of the periods presented would not have had a material impact on our consolidated financial statements.

Recent Accounting Pronouncements

In May 2014, the Financial Accounting Standards Board, or FASB, issued Accounting Standards Update, or ASU, No. 2014–09, Revenue from Contracts with Customers (Topic 606), and further updated through ASU 2016-12, which amends the existing accounting standards for revenue recognition. ASU 2014–09 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 guidance is effective for annual reporting periods, and interim periods within those years, beginning after December 15, 2017, for public entities and no later than for annual reporting periods beginning after December 15, 2018, for non–public entities. The new revenue standard may be applied retrospectively to each prior period presented or retrospectively with the cumulative effect recognized as of the date of adoption. While we continue to assess all potential impacts under ASU 2014-09, we do not believe adopting the new revenue recognition standard will materially impact the consolidated financial statements as we have not yet generated revenue.

In February 2016, the FASB issued ASU No. 2016-02, Leases (Topic 842), which supersedes the guidance in former ASC 840, Leases. 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, 2019, with early adoption permitted. The ASU is expected to impact our consolidated financial statements as we have certain operating lease arrangements for which we are the lessee. We are currently in the process of evaluating the impact the adoption of ASU 2016-02 will have on our consolidated financial position or results of operations. We expect that the adoption of this standard will result in the recognition of an asset for the right to use the leased facility on our consolidated balance sheet, as well as the recognition of a liability for the lease payments remaining on the lease. While the consolidated balance sheet presentation is expected to change, we do not expect a material change to our consolidated statement of operations.

In November 2016, the FASB issued ASU 2016-18, Statement of Cash Flows (Topic 230): Restricted Cash. The purpose of Update No. 2016-18 is to clarify guidance and presentation related to 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. The update is effective for fiscal years beginning after December 15, 2017, including interim reporting periods within those fiscal years. Early adoption is permitted. We are currently evaluating the impact of adopting this standard on the consolidated financial statements and disclosures, but do not expect it to be material.

In May 2017, the FASB issued ASU 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. It is effective for annual and interim periods beginning after December 15, 2017. Early adoption is permitted. We are currently evaluating the impact of adopting this standard on our consolidated financial statements and disclosures, but we do not expect it to have a significant impact.

FOUNDERS' VISION

We have embarked on a deeply personal journey to conquer neurodegenerative diseases. Collectively, these diseases represent one of the most significant medical challenges facing us today, impacting millions of people including our own families and friends. We are passionately dedicated to understanding these diseases. Our goal is nothing short of defeating neurodegeneration by harnessing the power of modern science and technology to discover and develop medicines that meaningfully improve the lives of patients and their families.

This is a formidable challenge and opportunity. Defeating degeneration – to us – is akin to summiting the tallest mountains. Hence the name Denali. For the longest time, mankind was unable to summit the highest peaks. But when the time was right, bold mountaineers succeeded, enabled by technological progress and a better understanding of the elements. We believe that the same is possible in neurodegeneration today.

We are well aware that we are taking on a major challenge, yet we believe that success is within our reach. Recent genetic insights, better diagnostic tools and the ability to engineer medicines to cross the blood-brain barrier are crucial components in defeating degeneration. We have contributed to and experienced firsthand the advances that are made possible by following breakthrough science. We believe that the field of neurodegeneration is now at the inflection point where oncology was years ago when genetic discoveries revealed biological pathways responsible for cancer growth that resulted in powerful drug targets, and biomarkers enabled the diagnosis and selection of patients for targeted treatment approaches. Similar success is within reach in neurodegeneration.

Just like the mountaineers who set out to conquer the highest peaks, it takes a courageous team with a singular focus and unrelenting persistence to succeed. At Denali, we have assembled an outstanding team of driven and passionate scientists and drug developers, and a powerful network of collaborators in academia and industry.

The science is breaking open, and the time is right to discover and develop effective medicines for neurodegeneration. Every day matters. To patients, to their families and to society at large. We invite you to join us on our journey to the summit.

Ryan Watts, Ph.D. CEO and Co-Founder	Alexander Schuth, M.D. COO and Co-Founder	Marc Tessier-Lavigne, Ph.D. Director and Co-Founder

BUSINESS

Overview and Strategy

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

Neurodegeneration represents one of the most significant unmet medical needs of our time, with few effective therapeutic options available for patients with Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, or ALS, and other neurodegenerative diseases. The burden of these diseases to patients and society is massive.

We believe the time is right to make a strong and ambitious effort to defeat neurodegeneration. We believe that we can succeed in a field that has seen limited success in the past, because of our team of experienced and passionately dedicated scientists and drug developers, our focused scientific strategy, and our proprietary blood-brain barrier, or BBB, platform delivery technology. We are developing a broad portfolio of targeted therapeutic candidates for neurodegenerative diseases and have recently initiated our first clinical trials. We commenced operations in May 2015.

Historical challenges in developing effective therapeutics for patients with neurodegenerative diseases included a scarcity of therapeutic targets due to a limited understanding of disease biology, insufficient uptake of therapeutics into the brain because of the BBB and few available biomarkers for target engagement, diagnosis, patient selection and tracking disease progression. In recent years, however, significant progress in each of these areas has been made, greatly increasing the likelihood of success of developing effective therapeutics for neurodegenerative diseases.

Our scientific strategy is guided by three overarching principles. We believe that the application of these principles will significantly increase the probability of success and will accelerate the timing to bring effective therapeutics to patients with neurodegenerative diseases:

Genetic Pathway Potential	We use recent advances in understanding human genetics and cell biology in neurodegeneration to select our therapeutic targets, disease pathways and biomarkers. We focus on genes that, when mutated, cause, or are major risk factors for, neurodegenerative diseases, which we refer to as degenogenes. These degenogenes directly point to important disease pathways, and we have initially selected three such pathways for which we have built significant scientific expertise: lysosomal function, glial biology and cellular homeostasis.
Engineering Brain Delivery	We engineer our product candidates to cross the blood-brain barrier and act directly in the brain. This engineering is designed to enable optimal concentration of a therapeutic in the brain in order to improve therapeutic target engagement. For large molecule product candidates, such as antibodies and enzymes, we have engineered a proprietary BBB platform technology. For small molecule product candidates, which are synthetically created therapeutics, we design and test appropriate molecular architectures to optimize their exposure 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. These biomarkers can be used as endpoints of efficacy in early clinical trials, with the goal of accelerating clinical development timelines. In addition, each of our therapeutic programs includes a patient selection strategy using biomarkers to identify and segment patients in order to increase the likelihood of success.

Our total portfolio currently consists of eleven programs. To prioritize the allocation of our resources, we designate certain programs as core programs and others as seed programs, and we currently have six core programs and five seed programs. Our core programs are at various stages of clinical and preclinical development, and we believe that each of these programs has the potential to result in either first-in-class or best-in-class products for neurodegenerative diseases.

In building and developing our portfolio, we are guided by the principles outlined above, which means that the therapeutic target or pathway for each program is genetically linked to neurodegenerative disease, our product candidates are being engineered to optimize brain delivery, and the clinical development plan will be enabled by biomarkers. We rigorously follow the science and employ the therapeutic modality that we believe is best suited to modulate the target pathway. Our product candidates currently include small molecules, antibodies and enzymes and may expand to include other modalities in the future.

To increase the probability of success, we make parallel investments in several product candidates and back-up candidates, and plan to advance only those candidates to the later stages of clinical development that show strong preclinical and early clinical data. We constantly strive to replenish, grow and optimize our portfolio through in-house discovery and external business development activities, in each case enabled by our strong internal research and development expertise and capabilities.

By developing a broad portfolio of product candidates, we can continuously apply learnings and tools across programs and leverage economies of scale in our research and development organization. Our target indications include diseases with large patient populations, such as Alzheimer's disease, as well as orphan indications, such as mucopolysaccharidosis type II, or MPS II, and ALS. We aim to increase the probability of success and accelerate clinical development timelines by using biomarkers and other tools to demonstrate an impact on relevant disease biology for proof of concept in early clinical trials.

We have development and commercialization rights to all of our core programs.

The following table summarizes key information about our core programs:

Program Target	Drug Candidate	Therapeutic Modality	Disease Indication	Preclinical Development	Clinical Development			Biomarker		
					Phase I	Phase II	Phase III	Preclinical Target Engagement	Clinical Target Engagement	Patient Selection
Lysosomal Function Pathway										
LRRK2	DNL201	Small Molecule	Parkinson's disease	Phase 1				✓	✓	✓
	DNL151	Small Molecule	Parkinson's disease	CTA accepted						
Alpha-Synuclein	ATV:aSyn	Antibody	Parkinson's disease, DLB, MSA	Preclinical				✓	●	●
Iduronate 2-sulfatase	ETV:IDS	Enzyme	MPS II (Hunter Syndrome)	Preclinical				✓	✓	✓
Glial Biology Pathway										
RIPK1	DNL747	Small Molecule	Alzheimer's disease, ALS	IND-Enabling				✓	✓	●
TREM2	ATV:TREM2	Antibody	Alzheimer's disease	Preclinical				✓	●	●
Cellular Homeostasis Pathway										
BACE1/TAU	ATV:BACE1/Tau	Antibody	Alzheimer's disease	Preclinical				✓	✓	✓

ATV: Antibody Transport Vehicle
ETV: Enzyme Transport Vehicle
ALS: Amyotrophic Lateral Sclerosis
DLB: Dementia with Lewy Bodies
MPS II: Mucopolysaccharidosis type II
MSA: Multiple System Atrophy

✓ Validated biomarker available
● Biomarker in development

Delivering therapeutics across the BBB has been a major obstacle to successful drug development in neurodegeneration, and is critical to enabling effective treatments. Protein

therapeutics, such as antibodies, have revolutionized the treatment of many diseases, but this class of medicines does not effectively cross the BBB and, therefore, currently has very limited therapeutic application to the treatment of neurodegenerative diseases. To address this limitation, we have developed proprietary drug delivery platform technologies, called ATV, or Antibody Transport Vehicle, and ETV, or Enzyme Transport Vehicle, designed to deliver large molecules across the BBB. We have achieved proof of concept for the ATV platform in a mouse model and have initial validating data from an ongoing study in nonhuman primates. We are currently optimizing and broadening this platform technology.

Our ATV and ETV platforms are modular BBB delivery technologies for large molecule therapeutics, including antibodies, enzyme and other proteins. Therapeutic candidates enabled by the ATV or ETV platforms are designed to engage specific BBB transport receptors, which are ubiquitously expressed in the brain capillaries and facilitate transport of proteins into the brain. In a mouse model across three studies designed to demonstrate proof of concept of the ATV platform, an antibody engineered with our ATV technology has demonstrated an average 20-fold greater brain penetration than a control antibody not enabled by this technology. In addition, initial data from an ongoing study in nonhuman primates designed to show proof of concept for the ATV platform demonstrates a robust and sustained pharmacodynamics, or PD, effect in the brain after intravenous dosing of an ATV-enabled antibody, while a standard antibody had minimal PD effect. The improvement in brain exposure may enable therapeutically relevant concentrations of our ATV antibody product candidates in the brain, making them potentially superior to traditional monoclonal antibody therapeutics.

We are currently developing several product candidates for multiple programs to advance to investigational new drug, or IND, enabling studies in preparation for human clinical trials. 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, or aSyn; iduronate 2-sulfatase, or IDS; triggering receptor expressed in myeloid cells 2, or TREM2; beta-secretase 1, or BACE1; and Tau.

We also follow a rigorous approach to designing small molecules to cross the BBB. DNL201 and DNL151, our small molecule inhibitors of leucine-rich repeat kinase 2, or LRRK2, and DNL747, our small molecule inhibitor of receptor interacting serine/threonine protein kinase 1, or RIPK1, have been specifically designed to cross the BBB.

LRRK2 is a degenogene that regulates lysosomal function, and mutations in LRRK2 are one of the most commonly known genetic causes of Parkinson’s disease. DNL201 is currently in a Phase 1 clinical trial. We submitted a CTA for DNL151 to the Netherlands Health Authority in October 2017 and it was accepted in November 2017. For DNL201, the FDA has allowed us to proceed with our Phase 1 clinical trial in healthy volunteers at doses that we believe will be sufficient to inhibit LRRK2 50% on average over the dosing period and should effectively normalize LRRK2 kinase activity. For exposures expected to be higher than this level, the FDA has issued a partial clinical hold on the DNL201 Phase 1 clinical trial, which the FDA may re-evaluate based on the safety and tolerability data generated by the study and data supporting the monitorability of the effects of DNL201.

RIPK1 is a regulator of microglial homeostasis and increased RIPK1 kinase activity drives neuroinflammation and cell necroptosis in immune cells and in the brain. RIPK1 inhibition has been shown to have beneficial effects in preclinical models of Alzheimer’s disease, ALS and other diseases. DNL747 is in IND-enabling preclinical studies and we plan to submit a CTA in early 2018.

We have assembled a team with deep scientific, clinical, business and leadership experience and expertise in biotechnology, and specifically in neurodegenerative diseases, who worked together at Genentech for many years prior to the founding of Denali. Our Co-Founder and Chief Executive Officer, Ryan J. Watts, Ph.D., is a world-leading drug developer and neuroscientist, with particular

expertise in BBB therapeutic delivery. Dr. Watts most recently led the neuroscience research team at Genentech and has led multiple discovery teams, including programs in Alzheimer's disease, Parkinson's disease and ALS. Our Co-Founder and Chief Operating Officer, Alexander O. Schuth, M.D., held various operational and leadership roles at Genentech for nearly ten years, including leading the partnering groups for neuroscience as well as technology innovation and diagnostics. Dr. Schuth has led more than 35 partnering transactions and a clinical stage development program. Our Co-Founder and director, Marc Tessier-Lavigne, Ph.D., is a world-leading neuroscientist, was formerly Chief Scientific Officer at Genentech and serves as President of Stanford University. Carole Ho, M.D., our Chief Medical Officer, brings over a decade of clinical development experience, most recently as Vice President, Non-Oncology Early Clinical Development at Genentech. Dr. Ho has overseen or contributed to more than ten IND filings and three drug approvals. Our Chief Financial Officer, Steve E. Krognes, brings over two decades of operational and corporate finance experience, most recently serving six years as Chief Financial Officer and member of the Executive Committee at Genentech. Mr. Krognes has led more than 40 strategic deals and led or contributed to several capital raising transactions.

Our leadership team is joined by approximately 125 employees, approximately two-thirds of whom hold Ph.D. or M.D. degrees. Together, they bring expertise across relevant disciplines, including neuroscience, BBB biology, genetics, oncology, immunology, translational science, antibody engineering, chemistry and biomarker development. Our development leadership team members have, collectively, led and contributed to more than 120 IND and clinical trial application, or CTA, filings. Our board of directors is comprised of several leaders from both academia and industry. Our directors include Vicki Sato, Ph.D. (Chair), retired Professor of Management at Harvard Business School, Doug Cole, M.D., Managing Director of Flagship Pioneering, Jay Flatley, Executive Chairman and retired Chief Executive Officer of Illumina, Robert T. Nelsen, co-founder and Managing Director of ARCH Venture Partners and David Schenkein, M.D., Chief Executive Officer of Agios Pharmaceuticals. Our directors collectively bring deep scientific knowledge and relevant industry experience.

Licenses and collaborations are central components of our strategy to build and advance our pipeline of product candidates. We have entered into arrangements with biopharmaceutical companies such as Genentech and F-star, numerous leading academic institutions such as Harvard University, Massachusetts General Hospital, Washington University in St. Louis, the University of California, San Diego and Vlaams Instituut voor Biotechnologie, foundations such as the Michael J. Fox Foundation, and patient-focused data companies such as 23andMe and Patients Like Me, to gain access to new product candidates, deepen our scientific understanding of certain areas of biology and enable and accelerate the development of our programs. We believe that accessing external innovation is important to our success and we plan to remain active in accessing external innovation through business development activities. Our goal is to be the most attractive partner for academic groups and companies in the field of neurodegeneration based on our singular focus, broad capabilities and ability to execute with scientific rigor and speed.

Our Approach to Defeating Neurodegeneration

Disease Overview

Neurodegenerative diseases are a collection of conditions defined by progressive nervous system dysfunction, degeneration and/or death of neurons causing cognitive decline, functional impairment and eventually death. Neurodegeneration represents one of the most significant unmet medical needs of our time, with the aging of the population and the lack of effective therapeutic options causing a rapid increase in the number of patients. The two most common neurodegenerative diseases are Alzheimer's disease, representing an estimated 60% to 70% of all dementias according to the World Health Organization, and Parkinson's disease. In the United States, 5.5 million people suffer from

Alzheimer's disease, as many as one million people suffer from Parkinson's disease (with 60,000 new patients being diagnosed each year), and more than 20,000 patients suffer from ALS, according to estimates from the Alzheimer's Association, the Parkinson's Disease Foundation, and the ALS Association, respectively.

The cost to society from neurodegenerative disease is massive. The direct costs of caring for individuals with Alzheimer's disease and other dementias in the United States will total an estimated $259 billion in 2017, and is projected to increase to $1.1 trillion by 2050, according to the Alzheimer's Association. In the United States, the total cost of care to patients suffering from Alzheimer's disease and other dementias far exceeds that of many other diseases, including cancer.

Genetic Pathway Potential

Advances in our understanding of the genetics, pathology and cell biology underlying chronic neurodegenerative diseases have identified pathways that trigger and/or contribute to disease onset and progression. Of particular importance is the progress in genetic sequencing where the dramatic reduction in the cost of deoxyribonucleic acid, or DNA, sequencing has recently contributed to the discovery of numerous genetic mutations that have been linked to neurodegeneration (Figure 1).

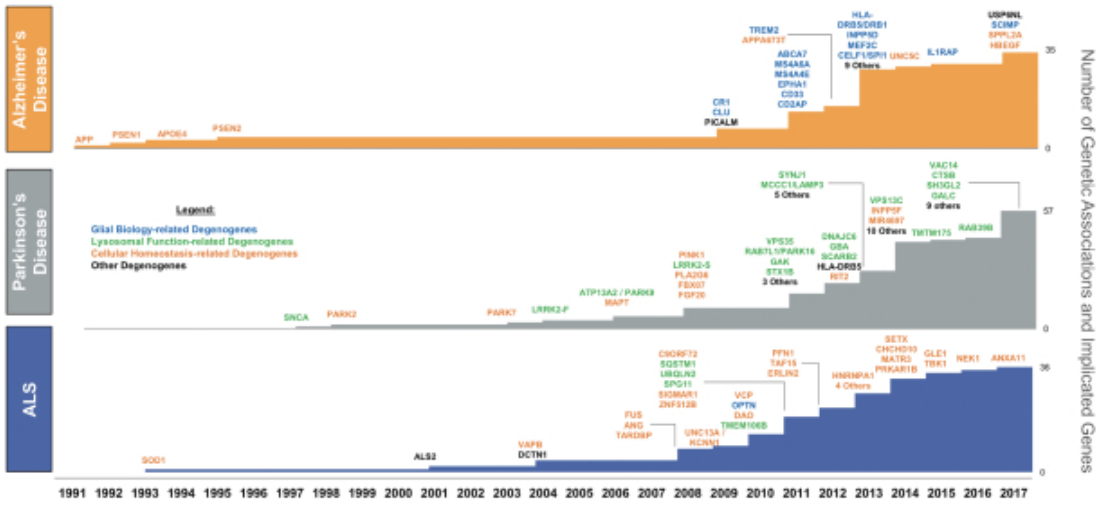
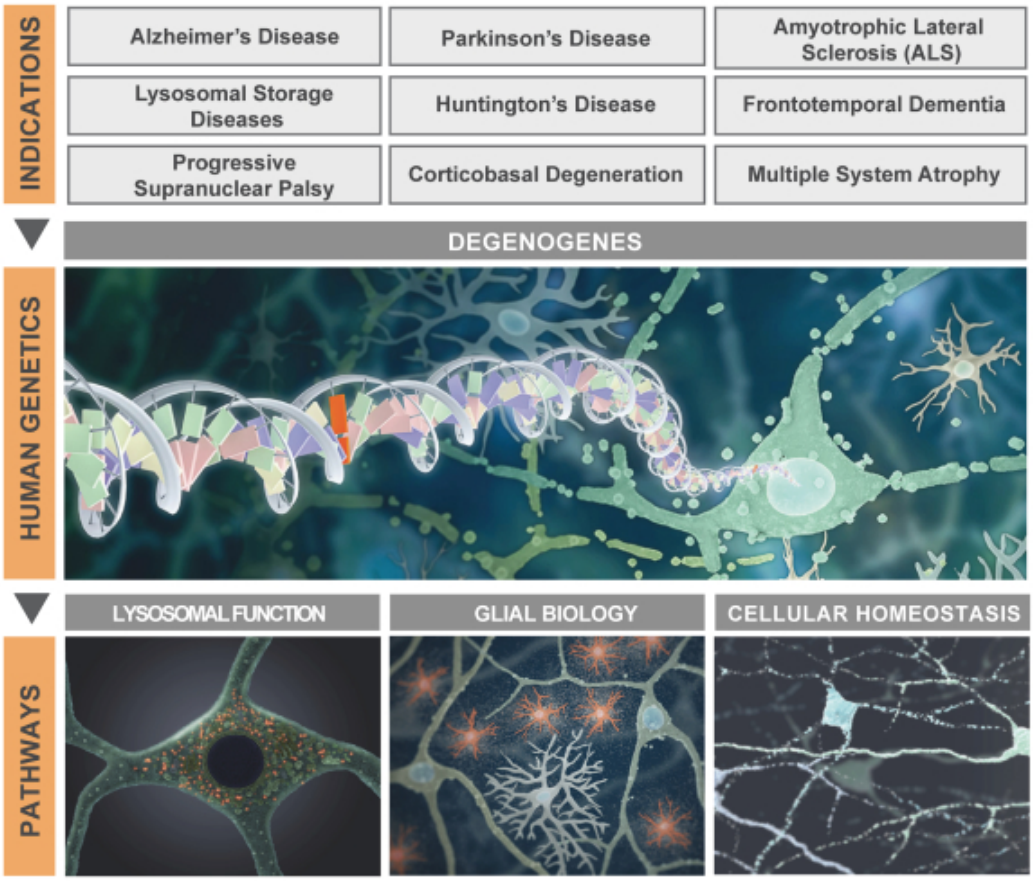


Figure 1: The number of associated genetic mutations linked to Alzheimer's disease, Parkinson's disease and ALS from 1991 to 2017. For genome-wide association studies, disease genes were selected based on genome-wide significance (p<5×10-8). Rare disease-causing and/or high penetrance mutations were included based on a p value of 1x10^-7 and replication in an independent cohort.

Human Genetics: Degenogenes

Prior to 2007, only a limited number of genetic mutations linked to Alzheimer's disease, Parkinson's disease and ALS had been identified. Since 2007, the number of genetic associations discovered in neurodegenerative diseases has grown rapidly, with more than 100 genes associated with these three neurodegenerative diseases collectively. The degenogenes directly point to important disease pathways that are disrupted in neurodegeneration, and are our scientific foundation for identifying and pursuing promising targets for drug development. We have chosen to initially focus on three such pathways: lysosomal function, glial biology and cellular homeostasis.



Disease Pathways

Lysosomal Function

The lysosomal system, the disposal and recycling compartment of the cell, is involved in the digestion and processing of proteins and lipids in brain cells. Dysfunction of the lysosomal system is associated with several neurodegenerative diseases, including Parkinson's disease and neurodegeneration in the context of lysosomal storage diseases, or LSDs. Degenogenes linked to lysosomal function include LRRK2, aSyn, and lysosomal enzymes, including IDS, and glucocerebrosidase, or GBA. Most LSDs result in rapid and aggressive neurodegeneration. We believe therapeutics designed to correct lysosomal dysfunction are a promising approach to broadly treat neurodegeneration.

Glial Biology

The human brain contains several types of glial cells, which are non-neuronal cells that maintain homeostasis, which is the ability of cellular or molecular pathways to seek and maintain a condition of equilibrium or stability within its internal environment when dealing with cellular stress and genetic variation, form myelin and support, protect and provide nutrition to neurons, and are critical to healthy brain function. A specific type of glial cells, microglial cells, which are macophages of the brain and spinal cord, act as the resident immune system in the brain. It has been recently discovered that

degenogenes implicate immune dysfunction in the brains of patients with Alzheimer's disease and other neurodegenerative diseases. These genes include TREM2 and numerous other genes that are highly expressed in inflamed microglia. We believe the impact of immune modulation in neurodegeneration is a promising approach to treating disease. Genetic and pathological data suggest that reversing defects in glial biology may significantly delay or halt the progression of some neurodegenerative diseases, such as Alzheimer's disease and ALS. Specifically, we and others have recently discovered that RIPK1, a kinase, which is an enzyme that catalyzes the addition of a phosphate group to substrates, usually proteins, downstream of the TNF receptor pathway, a highly validated biologic target in human disease, is overactive in inflamed microglia and several other cells in the brain. Blocking RIPK1 may reverse the hyper-inflamed nature of glia and restore normal function. Improving glial function and modulating the resident immune system in the brain represents a potentially attractive therapeutic strategy.

Cellular Homeostasis

Many degenogenes directly alter the homeostatic balance of brain cells. Specifically, defects in protein or ribonucleic acid, or RNA, homeostasis lead to the death of neurons and dysfunction of the nervous system. This includes spreading of protein aggregates resulting in proteinopathy, which is disease that results from disorders of protein synthesis, trafficking, folding, processing or degradation in cells, in Alzheimer's and Parkinson's diseases, and the aggregation of RNA binding proteins disrupting cellular stress response in Alzheimer's disease and ALS. The clearance of macromolecules in the brain is particularly susceptible to imbalances that result in aggregation and degeneration in nerve cells. For example, Alzheimer's disease pathology is characterized by the presence of amyloid plaques, which are accumulations of amyloid, or the complex proteins deposited in tissues that form the primary component of plaques characteristic of Alzheimer's disease, and neurofibrillary tangles, which are aggregates of hyperphosphorylated Tau protein that are a marker of Alzheimer's disease and other diseases known as tauopathies. Our approach is to create a bispecific antibody that targets both BACE1 and Tau, key proteins in the production of amyloid plaques and neurofibrillary tangles, which we believe has the potential for synergistic activity, restoring protein homeostasis with regards to the two most common Alzheimer's disease pathologies. We believe that therapies that correct defects in cellular homeostasis have the potential to halt or delay neurodegenerative disease progression.

Engineering Brain Delivery

The Blood-Brain Barrier Challenge

The human brain contains approximately 400 miles of blood vessels. These blood vessels are lined by closely linked endothelial cells to form the BBB, which protects the brain from toxins by regulating the transfer of proteins, nutrients and waste products. Delivery of therapeutics to the brain has been challenging as most small molecule drugs are actively excluded by efflux pumps, and brain uptake of therapeutic antibodies and recombinant enzymes is severely limited by their size. (Figure 2).

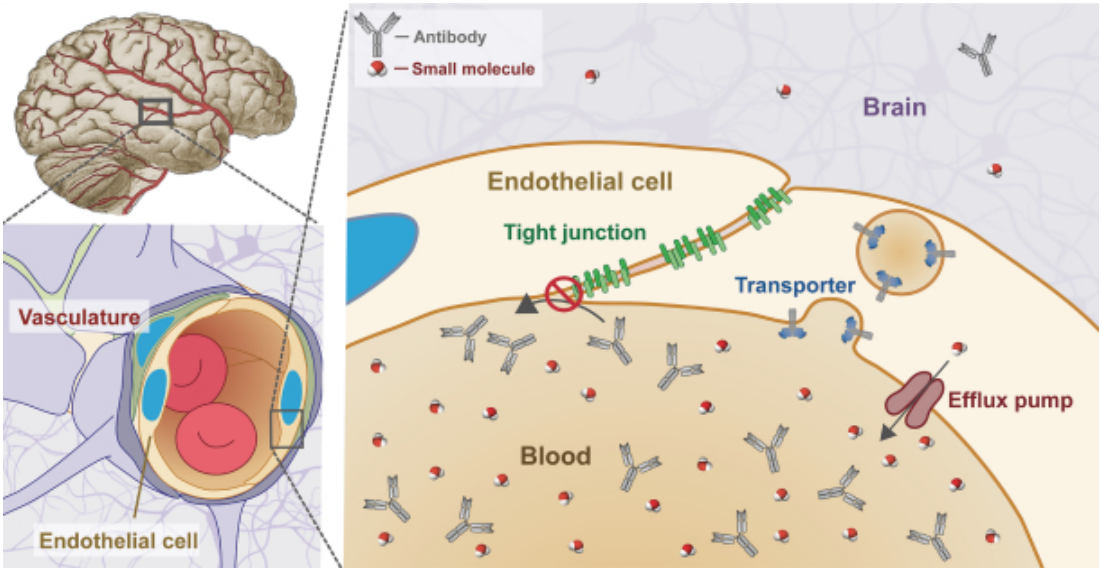


Figure 2. Schematic of the BBB. The specialized vessels of the brain represent a significant barrier for both small and large molecule therapeutics. Tight junctions between endothelial cells prevent the diffusion of large molecules while most small molecules are kept out of the brain by efflux pumps.

The protective nature of the BBB limits the passive uptake of small molecule and large molecule therapeutics in the brain. For example, the concentration of most therapeutic antibodies in the brain is only 0.1% of the concentration in the blood. We believe that this is one of the major reasons for the low success rates of clinical trials in neurodegenerative diseases to date. Engineering brain delivery of product candidates is critical to our success in developing effective therapeutics for patients with neurodegenerative diseases. Our product candidates are engineered to reach their intended targets in the brain at exposure levels that will provide a therapeutic effect, while having an acceptable safety profile. We do not plan to bring a product candidate into late-stage clinical testing unless it has shown sufficient brain concentration and target engagement in the brain in preclinical models and early-stage clinical trials.

Engineering Large Molecule Brain Delivery

For large molecules, including therapeutic antibodies and enzymes, we are developing proprietary platform technologies to actively transport these molecules across the BBB through receptor-mediated transcytosis, or RMT. RMT through the BBB is the process by which macromolecules in the blood bind to receptors on the endothelial cells that make up the BBB and are actively transported and released into the brain. Our large molecule transport vehicle, or TV, platform technology engineers BBB receptor binding into an Fc domain (Figure 3). We have selected transferrin receptor, or TfR, which is a highly-expressed BBB receptor that we believe has the ability to substantially improve brain uptake of therapeutic molecules. This construct can be integrated and fused to therapeutic molecules as described below, without disrupting the binding of transferrin to TfR.

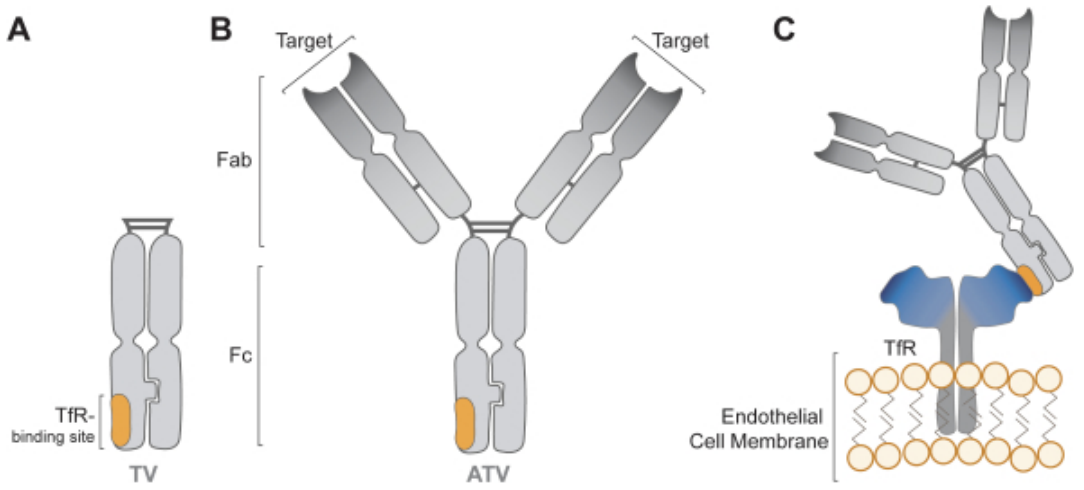


Figure 3. Schematic of the BBB large molecule Transport Vehicle (TV) technology. The TV platform technology contains BBB receptor (TfR) binding in the Fc domain (A). The TV can be fused to Fab arms constituting the Antibody Transport Vehicle (ATV) technology (B). ATVs bind to TfR, enabling TfR-mediated transcytosis and brain uptake (C).

Antibody Transport Vehicle

Our ATV platform technology utilizes the BBB receptor binding Fc domain to engineer bispecific and bivalent antibodies with improved brain delivery (Figure 4).

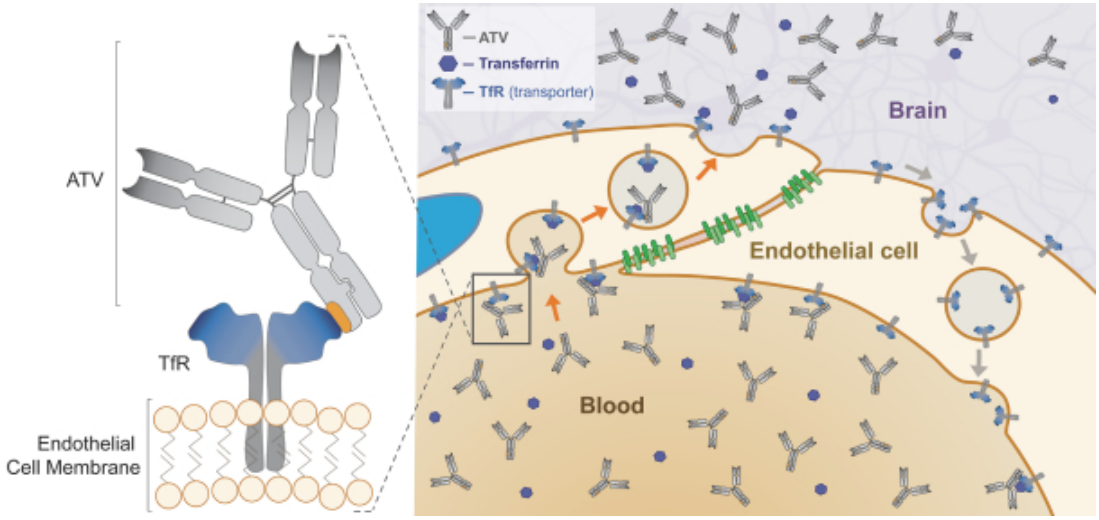


Figure 4. Schematic of receptor-mediated transport of ATV at the BBB. ATV molecules engage TfR on the blood vessel wall in the brain. Once bound, ATV is brought into vesicles that are transcytosed across the endothelial cell and released into the brain, thus substantially increasing antibody concentrations in brain. ATV binding to TfR does not disrupt the binding of transferrin to TfR.

We have achieved *in vivo* proof of concept for the ATV platform in mice whose genomes have been engineered to express a portion of the human TfR gene at a specific location, or human TfR knock-in mice, and we have generated initial validating data in an ongoing study in nonhuman primates.

In the human TfR knock-in-mouse model, we have completed three preclinical studies designed to demonstrate proof of concept for the ATV platform. Such studies have demonstrated an average 20-fold increased antibody uptake in the brain, compared to a control antibody (Figure 5).

As a result of a dramatic improvement in brain antibody uptake with the ATV, we observed a robust brain pharmacodynamic, or PD, response, which is the biochemical and physiological effect of a drug, as measured by reduction in levels of amyloid beta in brain. This represents a highly disease relevant proximal readout as amyloid beta levels are a primary driver of the amyloid plaque pathology in Alzheimer's disease. These data demonstrate that the brain concentrations achieved with the ATV platform are in excess of levels needed to mediate a therapeutic response. Without the ATV, the control antibody was unable to have a desired PD effect in the brain (Figure 5).

ATV-enabled antibodies also showed broad distribution in the brain, effectively crossing the BBB and associating with brain cells. Using brain imaging techniques, human IgG1 distribution was compared between a control anti-BACE1 antibody and ATV1:BACE1 (Figure 5). Images show robust localization of ATV1:BACE1 with cells in the brain after systemic delivery. These proof of concept data in a human TfR knock-in-mouse model demonstrate the ability of ATV to achieve therapeutic concentrations and broad distribution in brain.

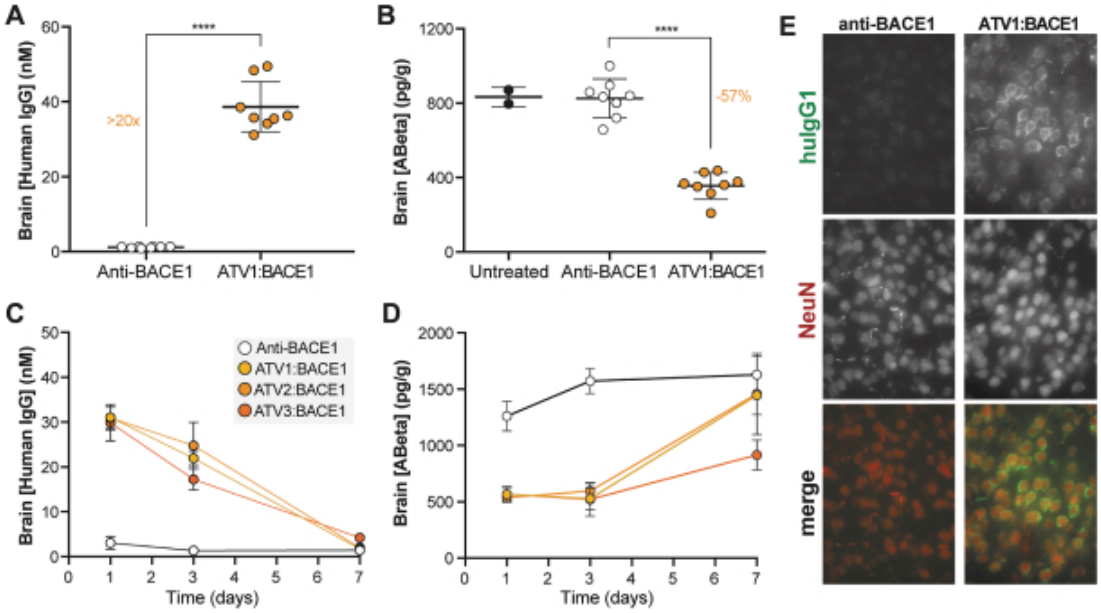


Figure 5: ATV therapeutics achieve robust brain uptake and pharmacodynamic activity in human TfR knock-in mice. Mice were injected with 50 mg/kg of anti-BACE1 or ATV1:BACE1. After 24 hours of circulation, brain antibody concentrations were compared between anti-BACE1 (1.2nM) and ATV1:BACE1 (38.6nM) (A). A significant reduction in brain Abeta levels (57%) was observed for mice injected with ATV:BACE1 compared to anti-BACE1, where no reduction was observed as compared to untreated mice (B). Mice were injected with 50 mg/kg of anti-BACE1, ATV1:BACE1, ATV2:BACE1 or ATV3:BACE1. All ATV:BACE1 variants show a significant increase in brain uptake at 1 and 3 days post-dose as compared to anti-BACE1 (C). Significant brain Abeta reduction was observed for all ATV:BACE1 variants at 1 and 3 days post-dose, and for ATV3:BACE1 at 7 days post-dose, as compared to anti-BACE1 (D). Immunohistochemistry staining of brain sections from mice injected with either anti-BACE1 or ATV1:BACE1 24 hours post-dose. Robust and broad neuronal distribution of systemically administered ATV1: BACE1, but not anti-BACE1 is observed (E). HulgG1 labels antibody; NeuN labels neurons; ** indicates p<0.0001.**

To further validate the ATV platform, we initiated an *in vivo* study in nonhuman primates with an ATV designed to bind to cynomolgus monkey TfR (ATV4:BACE1). Initial data from this ongoing study

demonstrates a robust and sustained brain PD response as measured from fluid taken from brains of living monkeys (Figure 6). When measuring drug activity in blood (plasma) versus brain (CSF), both anti-BACE1 and ATV4:BACE1 show robust activity in the blood, however only the ATV enabled antibody (ATV4:BACE1) demonstrated robust and sustained PD activity in the nonhuman primate brain. We believe these *in vivo* proof of concept data in nonhuman primates provide support for the translatability of the ATV platform for human studies.

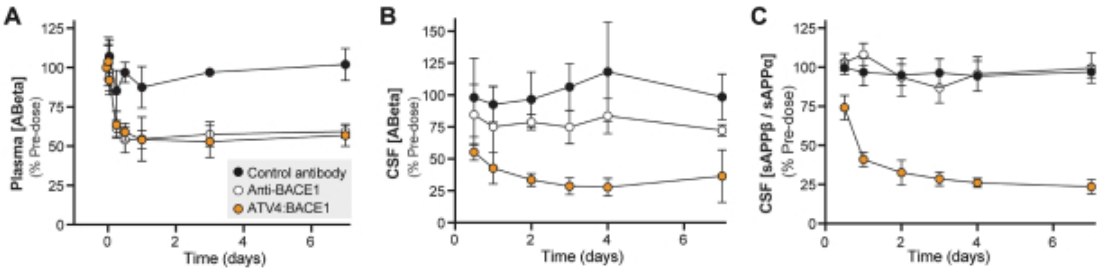


Figure 6. ATV therapeutics achieve CNS pharmacodynamic activity in nonhuman primates. Cynomolgus monkeys were systemically injected with 30 mg/kg of control antibody, anti-BACE1, or ATV4:BACE1. In plasma, anti-BACE1 and ATV4:BACE1 equally reduce Abeta levels (A). In CSF, a robust and sustained reduction in CSF Abeta (B) and soluble APPbeta/APPalpha ratio (C) was observed in monkeys injected with ATV4:BACE1 compared to control antibody. In contrast, anti-BACE1 has minimal impact on CSF Abeta and APPbeta/APPalpha levels (C).

Enzyme Transport Vehicle

Our ETV platform utilizes the same RMT approach as our ATV platform to deliver enzymes across the BBB. One potential application of this technology is the neurological component of LSDs. The ETV platform technology is an Fc enzyme fusion in which the TfR binding is engineered into the Fc domain (Figure 7). The high modularity of the platform make it uniquely well suited for delivery of enzymes across the BBB. The ETV enables different fusion formats with one or two enzymes. The characteristics of the ETV platform are also applicable to proteins and peptides that may be fused to the platform for other indications.

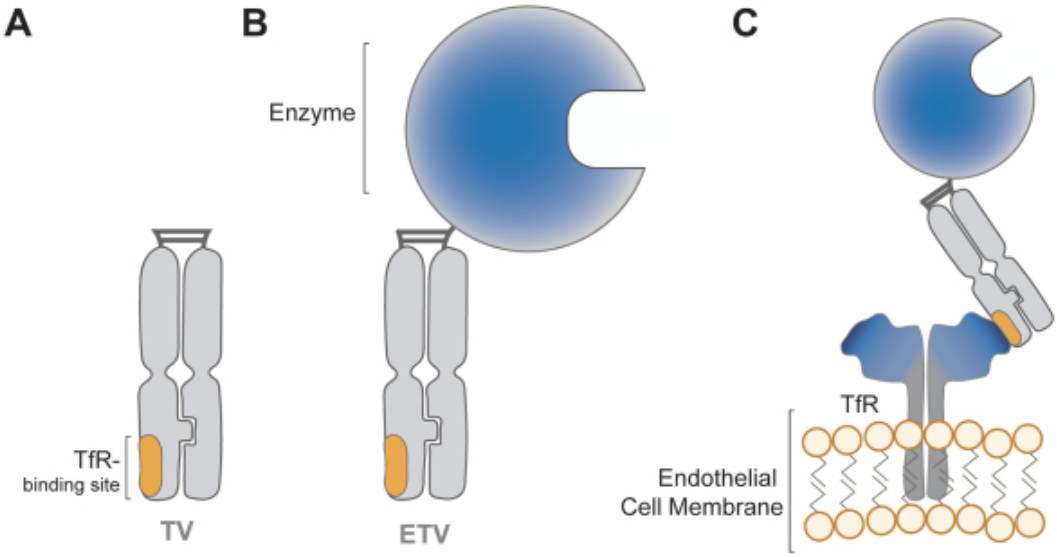


Figure 7: Engineering brain delivery using the ETV platform. The ETV platform technology contains BBB receptor (TfR) binding in the Fc domain (A) fused to an enzyme (B) to enable transport of enzymes into the brain through TfR-mediated transcytosis (C).

Platform Technology Development and Applications

We are advancing our ATV and ETV platforms through further preclinical studies in mice and non-human primates. We plan to commence IND-enabling studies with multiple preclinical product candidates in 2018 and initiate clinical trials in 2019. We are also combining our proprietary human TfR knock-in-mice model with disease-specific animal models in order to more precisely assess the potential of our ATV-enabled therapeutic candidates in relevant disease models. We expect that this will give us the ability to perform pharmacokinetic/pharmacodynamic, or PK/PD, and efficacy studies and to quantitatively demonstrate the advantages of antibodies and proteins delivered using our ATV platform technology.

To enable the development of our ATV and ETV platform technologies, we have entered into a strategic licensing and collaboration agreement with F-star. This collaboration gives us the ability to obtain exclusive access to an intellectual property portfolio covering engineering of the Fc region of antibodies for use with specific targets, such as the TfR. The collaboration enhances our own protein engineering capabilities by leveraging F-star's more than 10 years of experience in this area. Our collaboration is focused on TfR binding with the option to expand the collaboration to develop two additional BBB receptor targets.

We believe that our ATV and ETV platforms are also broadly applicable beyond neurodegeneration and LSDs to improve delivery of antibodies to treat other brain diseases, including cancer. We currently are not pursuing these additional indications, but we may do so independently or with partners in the future.

Engineering Small Molecule Brain Delivery

We are focused on engineering small molecule therapeutics that achieve exposure levels in the brain sufficient to bind to protein targets and drive a therapeutic effect. Efficacious orally administered small-molecule medicines for brain diseases must be readily absorbed from the gut into the blood and penetrate the BBB while avoiding transporter-mediated efflux (Figure 8). It has been estimated that approximately 98% of small molecule drugs do not cross the BBB.

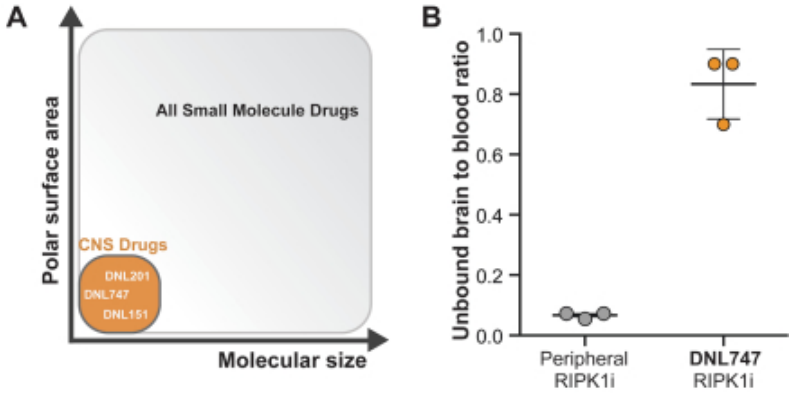


Figure 8: Generation of brain penetrant small molecules. The molecular properties compatible with CNS drugs are significantly more restricted than those generally used to design small molecule drugs, including tight restrictions on

molecular weight and total polar surface area (A). This figure is not to scale. An example of how molecular properties influence brain penetration is shown in (B), where our lead RIPK1 inhibitor DNL747 displays a brain to blood ratio of ~0.8 while a benchmark periphery-restricted RIPK1 inhibitor displays a ratio of ~0.05.

Our small molecule drug discovery scientists have many years of experience designing small molecules for brain diseases, including DNL151, one of our lead LRRK2 inhibitors, and DNL747, our lead RIPK1 inhibitor, both of which have demonstrated strong brain exposure and confirmed target engagement in preclinical studies.

Biomarker-Driven Development

Translational science is the process of gathering and interpreting data obtained from cellular and animal models to inform the design and expected clinical outcome of future patient studies. In the field of neurodegeneration, this has been particularly difficult due to a lack of validated biomarkers and predictive animal models to confirm drug exposure and target engagement in brain tissue, as well as clinical disease progression and response. Historically, many programs have advanced into late-stage clinical trials prior to demonstrating a relevant biologic response.

We define biomarker goals at every phase of development, including prior to the filing of an IND. As molecules transition from the discovery phase to early clinical development, we focus on refining our understanding of the relationship between the PK/PD response and modulation of target biology using target engagement and other relevant biomarkers. This integrated approach allows for the design of rigorous and informative pharmacology experiments.

In addition, we strive to develop a patient selection strategy guided by a genetic rationale and understanding of target biology for each of our programs. With this approach, we seek to increase the probability of success and make drug development more cost efficient by attempting to minimize avoidable errors in dose selection and study design that are impactful and costly in Phase 2 and Phase 3 clinical trials.

Approach to Target Engagement and Dose Selection

As part of our strategy, we are developing proprietary reagents, which are substances used to characterize or quantify a biological process or component, and assays, which are procedures to assess the amount or activity of a target entity, to enable biomarkers for each of our core programs. These biomarkers, which are relevant for both animal models and human trials, are critical for patient selection, predicting and measuring target engagement, supporting dose selection and enabling decisions on progression of product candidates to the next phase of development. Because potential targets of interest are in the brain, it is important to develop reagents that can assay specific biomarkers not only in the blood but also in the cerebrospinal fluid, or CSF, and the brain. By enabling biomarkers that are present in both animal models and humans, we are able to create a clinical strategy whereby measurements of exposure and target engagement in animals allows for better clinical translation and PK/PD modeling for human trials.

An example of this approach is reflected in our LRRK2 program. We developed validated assays of LRRK2 kinase activity that measure phosphorylation of LRRK2 at Serine 935, or pS935, or the phosphorylation of the LRRK2 substrate Rab10, or pRab10. In a preclinical monkey model, we have demonstrated that, following a single dose of a brain penetrant LRRK2 kinase inhibitor, there is a dose dependent reduction of LRRK2 kinase activity observed in the brain that is reflected in LRRK2 kinase inhibition in peripheral blood mononuclear cells, or PBMCs. Experiments such as this establish a relationship between peripheral (e.g. blood) and central (e.g. brain) target engagement, enabling the prediction of central target engagement in humans with measurements of blood and CSF drug exposure in conjunction with a peripheral assay for LRRK2 kinase activity.

Development of blood based assays potentially enables an assessment of target engagement in the clinic as early as first-in-human Phase 1 trials in healthy volunteer subjects. We have developed human assays using healthy control blood samples to assess performance of clinical candidates, and we regularly refine the reliability and quantitative rigor of our target engagement assays. After development of prototype assays, high sensitivity, high throughput, and quantitative platform based assays are developed for clinical use.

In the design of our Phase 1 trials, we plan to integrate our target engagement biomarker data with pharmacokinetic, or PK, analysis, which is the time course of drug absorption, distribution, metabolism and excretion, from both the plasma and CSF to determine the relationship between dose, time and drug response. We develop an integrated exposure response model that enables tailoring of the dose selection for future patient studies. This model relies on the quantitative PD biomarkers assessment enabled by the development and refinement of reliable assays, described above. We plan to progress product candidates that show robust target engagement at well-tolerated doses in early clinical development into our proof of concept trials.

We have identified target engagement biomarkers for all six of our core programs. When practicable, we are developing patient selection biomarkers for our programs to enable identification of patients with the relevant disease biology and stage of disease likely to benefit from targeted therapy in order to increase the likelihood of success of clinical trials. Ultimately, by reducing the number of patients that are likely to experience a low treatment response, we expect to positively impact market acceptance of these targeted therapies driven by high and meaningful response rates within the targeted population as defined by the patient selection biomarkers. In certain indications, regulatory approval may limit the market of a product candidate to target patient populations when patient selection biomarkers are used. In these indications, regulatory authorities may require us to run additional clinical trials prior to expanding the label for approval that includes a broader patient population.

We plan to leverage the target engagement biomarker data resulting from Phase 1 healthy volunteer studies to determine target engagement and guide dose selection in patients. We have invested in capabilities to obtain blood samples and other samples from patients with Alzheimer’s disease, Parkinson’s disease, and ALS to improve our prediction of relevant exposure-response relationships and support the design of future patient clinical trials. The data from these biomarker assessments using proprietary assays and PK analyses are critical to dose selection in the design of Phase 1b and Phase 2 clinical trials.

Approach to Pathway Engagement and Disease Progression

Our approach to building expertise in pathway biology enables identification of candidate pathway biomarkers that can be assessed in our clinical studies to understand pathway engagement and may serve as potential endpoints. An example of this approach is outlined in Figure 9. In this example, development of reagents for fluid biomarkers (for instance, Rabs) as well as imaging biomarkers (for instance, dopamine transporter imaging, or DAT) are being evaluated.

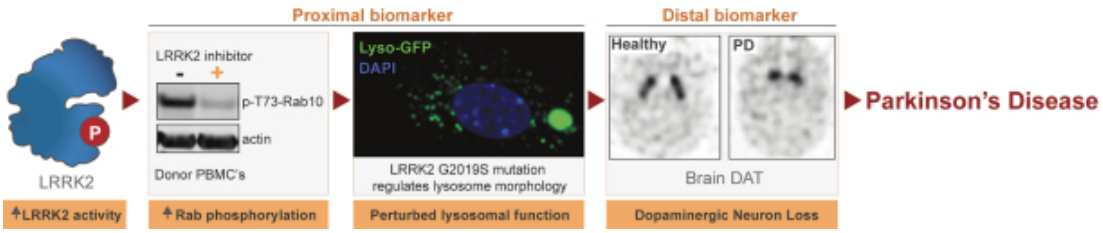


Figure 9: Example of strategic approach to generate biomarkers of LRRK2 target engagement (i.e., Rab phosphorylation), pathway modulation (i.e., lysosomal function) and disease modification (i.e. brain DAT imaging) to build evidence of relevant biologic activity that will impact clinical outcomes.

Approach to Patient Selection

In the past, the diagnosis of neurodegenerative diseases has generally relied on clinical diagnosis, without direct confirmation of pathology. This approach is inherently prone to errors, including misdiagnosis. The lack of pathology-confirming biomarkers has led to the enrollment of patients in clinical trials for neurodegenerative diseases who were very unlikely to respond to treatment, including patients who in fact did not have the disease being studied.

Our focus on degenogenes and the underlying biology of genetic pathways enables more precise selection of patients compared to relying only on a clinical diagnosis. For example, genotyping Parkinson's disease patients for LRRK2 mutations is a strategy for patient selection. Alzheimer's disease is likely a heterogeneous disease with different biology contributing to common downstream effects, including amyloid deposition in the brain. In Alzheimer's disease, understanding the biology of patient subsets defined by APOE4 genetic status as well as inflammatory biomarkers highlighted by Genome Wide Association Studies, provides hypotheses for development of novel biomarkers that can identify the subset of patients most likely to benefit from a particular therapeutic approach.

By utilizing biomarkers and genetic information, we can better target and select the best patient population for our clinical trials and product candidates.

Our Portfolio

As described above, our portfolio currently comprises six core programs and five seed programs. In addition, we continually evaluate additional targets for inclusion as seed programs, while we seek to maintain a rigorous process of prioritization and resource allocation to maintain an optimal balance between aggressively advancing lead programs and ensuring replenishment of the portfolio. We discuss our six core programs in further detail below.

Lysosomal Function Pathway Programs

LRRK2 Inhibitor Program

The two most advanced product candidates are potent, selective and brain penetrant small molecule LRRK2 inhibitor product candidates for Parkinson's disease. DNL201 is currently in a Phase 1 clinical trial. DNL151 has completed IND-enabling preclinical studies. We submitted a CTA for DNL151 to the Netherlands Health Authority in October 2017 and it was accepted in November 2017.

Therapeutic Rationale

Lysosomal dysfunction is a central pathology of Parkinson's disease. Genetic mutations in several proteins associated with Parkinson's disease, including LRRK2, GBA and aSyn, disrupt normal

lysosomal function and contribute to the formation of Lewy bodies, which are intracellular aggregates containing aSyn proteins, and neurodegeneration (Figure 10). LRRK2 regulates lysosomal function by phosphorylating Rab proteins, which control intracellular lysosomal trafficking (Figure 11). Mutations in the LRRK2 gene that cause Parkinson's disease increase both LRRK2 kinase activity and the phosphorylation of Rab proteins. Excessive phosphorylation of Rab proteins alters Rab localization and disrupts normal lysosomal movement and maturation. Inhibition of LRRK2 kinase activity with a LRRK2 kinase inhibitor reduces Rab phosphorylation and restores normal lysosomal morphology.

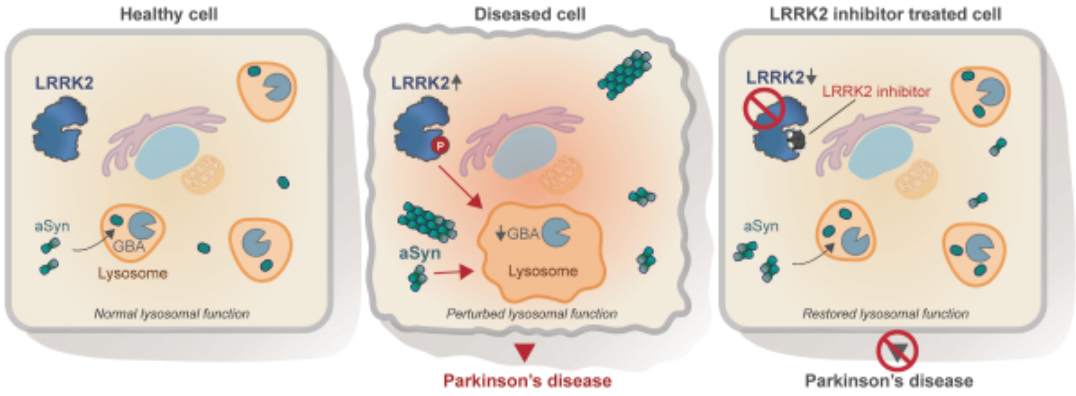


Figure 10: LRRK2 acts in healthy cells to maintain normal lysosomal function. Excessive LRRK2 activation or expression reduces lysosomal function and contributes to the progression of Parkinson's disease. Lysosomal dysfunction in Parkinson's disease can also be caused by high levels of aSyn and by loss of function of GBA. LRRK2 inhibition can restore normal lysosomal function and reduce toxicity in Parkinson's disease models.

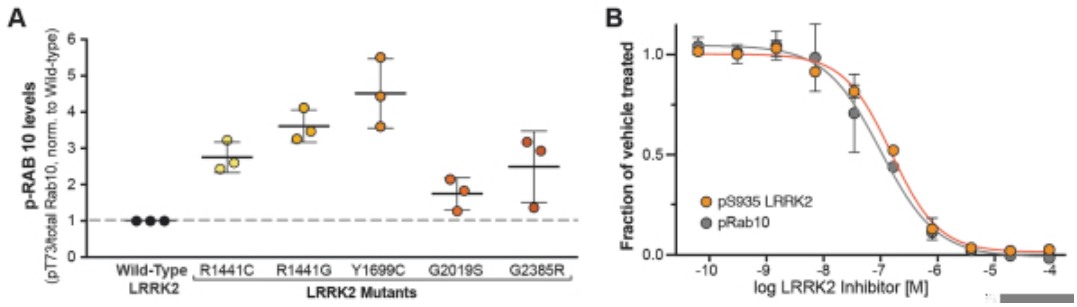


Figure 11. Phosphorylated Rabs are a novel marker of LRRK2 activity. Multiple distinct LRRK2 mutations result in elevated phosphorylation of the downstream marker Rab10 (A), while inhibition of LRRK2 results in a dose-dependent inhibition of Rab10 phosphorylation that is comparable to the inhibition of LRRK2 phosphorylation on Serine 935 (B).

Inhibition of LRRK2 kinase activity has been shown to be beneficial in several cellular and *in vivo* models. The most common LRRK2 mutation, G2019S, is a point mutation that results in increased kinase activity, abnormal lysosomal biology and an increased risk of Parkinson's disease. LRRK2 G2019S expression in cells from transgenic mice or other cell lines reduces the lysosomal capacity of the cell, leading to decreased lysosomal function. These defects are dependent on LRRK2 kinase activity, and treatment with DNL201 rescues the observed lysosomal phenotype (Figure 12). LRRK2 G2019S expression in neurons leads to a similar lysosomal phenotype and also results in reduced neurite outgrowth, an effect that can be rescued with LRRK2 kinase inhibition.

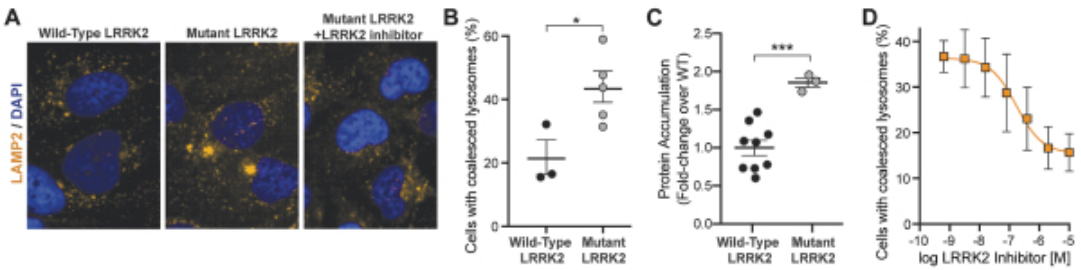


Figure 12: Effect of LRRK2 mutations on lysosomes. Cells expressing LRRK2 with the G2019S mutation display coalesced and dysfunctional lysosomes that are not present in cells expressing normal (WT) LRRK2. The presence of these abnormal lysosomes can be reversed through treatment with LRRK2 kinase inhibitors (A). Lysosomes can be visualized via LAMP2 (orange) while DAPI (blue) labels nuclei. This lysosomal defect is quantified in (B), and correlates with a loss of lysosomal function as measured by the amount of protein degradation (C). Inhibition of LRRK2 with our compounds results in a dose-dependent rescue of lysosomal abnormalities (D). * indicates p<0.05, * indicates p<0.001.**

Patients with Parkinson's disease often have high levels of activated immune cells and inflammatory markers in blood and CSF. LRRK2 is highly expressed in glia and other immune cells, and LRRK2 kinase inhibition or knockout of the LRRK2 gene protects animals in inflammatory disease models, including rhabdomyolysis kidney injury, exposure to the bacterial toxin lipopolysaccharide, and experimental autoimmune uveitis. These findings suggest that LRRK2 inhibition may reduce the deleterious inflammatory responses associated with Parkinson's disease.

Mutations in the aSyn gene and aSyn overexpression may cause certain forms of familial Parkinson's disease, and aSyn oligomers are thought to accelerate neurodegeneration. *In vitro* and *in vivo* models that employ aSyn oligomers to cause inflammation and cellular and lysosomal dysfunction are commonly used as preclinical models of Parkinson's disease. Microglia from mice that do not express LRRK2 absorb and degrade aSyn more effectively than wild-type mouse microglia. In most cell and mouse aSyn models, reducing LRRK2 kinase activity or expression protects animals from neurodegeneration and excessive inflammation. These findings provide further support for inhibition of LRRK2 activity as a therapeutic strategy to treat Parkinson's disease.

Patient Population

Mutations in the LRRK2 gene are the most frequent cause of familial Parkinson's disease and, in addition, are present in 1 to 2% of patients with sporadic Parkinson's disease in the United States. In total, we estimate that LRRK2 mutations account for approximately 2% to 3%, or 20,000 to 30,000, of one million total Parkinson's disease patients in the United States. The most common LRRK2 mutation, G2019S, is a point mutation that results in increased kinase activity and abnormal lysosomal biology. In addition to G2019S, six other pathogenic LRRK2 mutations resulting in increased LRRK2 expression or function have been strongly linked to Parkinson's disease.

While mutations that increase LRRK2 kinase activity provide the most direct link to the therapeutic rationale, other genetic drivers of Parkinson's disease, such as mutations in GBA and aSyn, are also associated with lysosomal dysfunction, which may be addressed through LRRK2 inhibition.

Furthermore, patients with idiopathic Parkinson's disease, i.e. patients with a clinical diagnosis of Parkinson's disease without a known genetic cause, typically also show signs of lysosomal dysfunction. Thus, as lysosomal dysfunction is a central pathology in patients with and without known

genetic drivers of disease, inhibition of LRRK2 may be a therapeutically beneficial approach for most patients with Parkinson's disease (Figure 13).

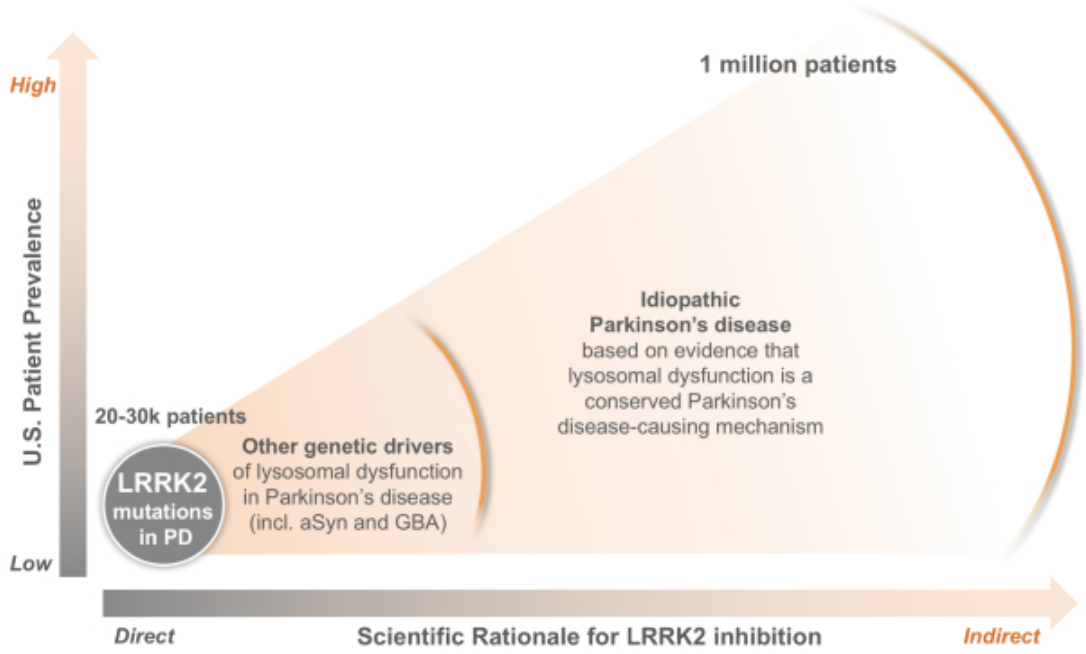


Figure 13: Target Parkinson's disease patient populations for LRRK2 inhibitor. (Figure not to scale)

Pharmacological Properties and Brain Exposure

We have a broad portfolio of potent, selective and brain penetrant LRRK2 inhibitors with attractive pharmacological properties. Our lead product candidates, DNL201 and DNL151, are selective, orally available, brain-penetrant, reversible small molecule inhibitors of LRRK2. The pharmacology of both product candidates has been investigated in a broad range of biochemical and cell-based *in vitro* assays, and both product candidates have been shown to inhibit LRRK2 activity with low nanomolar potency in human blood cells.

Both DNL201 and DNL151 displayed comparable potency of LRRK2 inhibition in both LRRK2 mutation carriers and non-carriers, with a trend to increased potency in G2019S mutation carriers (Figure 14).

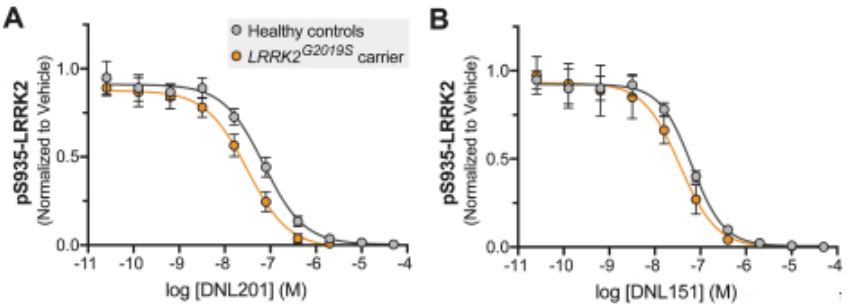


Figure 14. Treatment of peripheral blood mononuclear cells (PBMCs) derived from LRRK2 mutation and healthy non-carriers with our LRRK2 inhibitors. Both DNL201 (A) and DNL151 (B) demonstrated a small increase in potency in G2019S mutation carriers.

We have completed extensive preclinical PK and PK/PD evaluations of DNL201 and DNL151. Based on these data and preclinical modeling of clearance, the expected human half-life is compatible with BID (twice daily) dosing and QD (once daily) dosing for DNL201 and DNL151, respectively. Comparable unbound plasma and CSF exposures were observed in rodents and monkey, demonstrating that the compounds are brain penetrant and can achieve meaningful and sustained brain exposures as shown in a representative dataset for DNL201 (Figure 15). PD was characterized using a marker of LRRK2 kinase activity, pS935. Inhibition of pS935 in PBMCs is comparable to inhibition of pS935 in the brain after 28 days of dosing of DNL201 in monkey, demonstrating that peripheral blood inhibition of pS935 can be used to predict inhibition of pS935 in the brain. In toxicology studies in rodent and monkey, administration of DNL151 and DNL201 consistently resulted in dose-dependent inhibition of LRRK2 activity in peripheral tissues and in brain as measured by a reduction of pS935 LRRK2 levels.

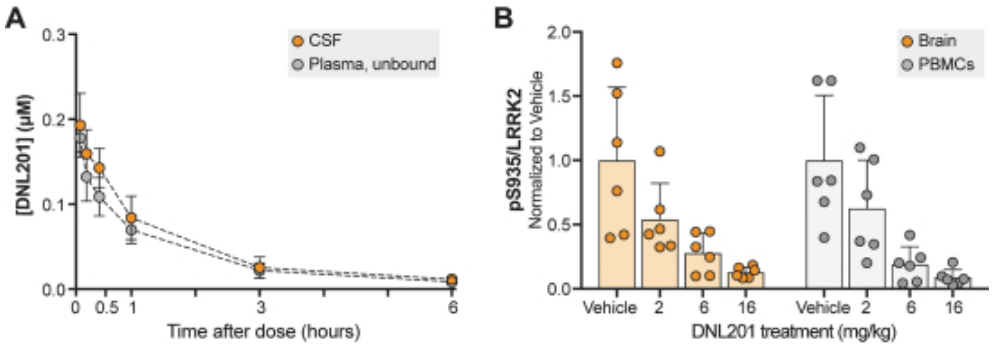


Figure 15. Exposure of DNL201 in monkey CSF and plasma (unbound) and activity of DNL201 in brain and PBMCs. Unbound DNL201 concentrations in plasma and CSF following intravenous administration of DNL201 are comparable (A). Similar pS935 inhibition is observed in PBMCs and brain 24 hours after the last dose is given (B).

The preclinical safety profiles of DNL201 and DNL151 have been characterized in a comprehensive battery of non-GLP and GLP safety pharmacology and single dose and repeat dose *in vivo* toxicology evaluations in rat and monkey. These PK, PK/PD and preclinical safety data indicate that both molecules can achieve significant levels of inhibition of LRRK2 kinase activity in the brain at dose levels that can be evaluated in clinical trials.

The definitive 28-day GLP toxicity studies for both DNL201 and DNL151 were conducted in monkey and rat. For these studies, the monkey was selected as the non-rodent species in order to fully characterize previously reported data showing that multiple structurally distinct LRRK2 inhibitors cause pharmacologically-driven lung histology changes. A target-related kidney finding has also been previously reported in rodents dosed with LRRK2 inhibitors and in rodent transgenic models. These findings consist of accumulation of lipid membranes of lysosomal organelles (lamellar bodies) in cells in the lung and vacuolization (droplets) in the kidney, also a lysosomal phenotype. In summary, these histologic changes related to loss of function or inhibition of LRRK2 kinase did not impact life span in these animal models or have obvious functional effects. Mice that lack LRRK2 protein (LRRK2 knockout mice) live a normal life span with no obvious pulmonary or renal function abnormalities despite accumulation of lamellar bodies in the lung and droplets in the kidney. In a Michael J. Fox Foundation, or MJFF, sponsored study, three distinct LRRK2 kinase inhibitors produced a mild accumulation of the previously described lamellar bodies in the lung. After 15 days of dosing, there were no functionally significant alterations in any pulmonary function endpoint examined, including lung diffusion capacity, lung compliance, and forced vital capacity. In addition, after cessation of dosing, the findings were fully reversible. The conclusion of this MJFF sponsored study was that the morphological changes observed in the lungs of LRRK2 kinase inhibitor treated monkeys may not prevent the clinical evaluation of the therapeutic potential of LRRK2 kinase inhibitors in Parkinson's disease. We have further characterized the cellular effects of LRRK2 kinase inhibitors and believe that the histological changes seen with LRRK2 inhibition in kidney and lung are due to direct effects on lysosomal morphology that are related to the therapeutic potential of LRRK2 inhibition in treatment of Parkinson's disease. In a cellular model of Parkinson's disease, a LRRK2 G2019S cell line model, cellular abnormalities due to defects in lysosomal function are characterized by morphologic abnormalities including a reduced number of lysosomes and abnormally large lysosomes. With inhibition of LRRK2 in this cellular model, the altered lysosomal morphology can be corrected, and with full inhibition, increased lysosomal number and area is observed, similar to the changes seen in rodent models lacking LRRK2 function and in monkeys dosed with LRRK2 inhibitors.

In the 28-day GLP toxicity studies for DNL201 in rats and monkeys, no adverse findings were observed at doses with exposure multiples >9-fold higher than the predicted maximum concentration, or Cmax, at therapeutic dose levels. In both rats and monkeys, findings were determined to be reversible following a 28-day treatment free period. On-target histological changes of vacuolation in rat kidney and lamellar body accumulation in monkey lung with DNL201 dosing were observed as expected. In prior pilot toxicity studies for DNL201, which were designed to define the maximum tolerated dose of DNL201 in rat, severe clinical signs were observed at high doses where the observed exposure is well in excess of that required for therapeutic efficacy (e.g. Cmax is ^{3}20-fold higher than the predicted Cmax at therapeutic dose levels). These severe clinical signs included labored breathing and severe hypoactivity. Results from an investigative preclinical cardiovascular study performed by us in rats supports that these severe clinical signs are caused by a monitorable cardiovascular mechanism characterized by a mild drop in blood pressure and increased heart rate after the first and second dose in all animals studied, followed by more profound drops in blood pressure associated with severe clinical signs after the third dose in a subset of rats. In this study, the rats recovered from the clinical signs after cessation of dosing.

Based on these studies, the U.S. Food and Drug Administration, or FDA, approved the Phase 1 clinical trial for DNL201 but placed DNL201 on a partial clinical hold in order to impose an exposure cap. With the current exposure cap, we are able to dose to an exposure that we believe will be sufficient to inhibit LRRK2 50% on average over the dosing period and should effectively normalize LRRK2 kinase activity. The FDA may re-evaluate the exposure cap for this study, and may potentially raise it, based on the safety and tolerability data generated by the study as it progresses as well as the data supporting the monitorability of the effects of the study. If the exposure cap is not lifted in the Phase 1 clinical trial, we will not be able to evaluate doses and exposures that would potentially

achieve higher degrees of LRRK2 kinase inhibition, which may negatively impact the development of DNL201.

For DNL151, in the 28-day GLP toxicity studies, no adverse findings were observed at doses with exposure multiples >11-fold higher than the predicted Cmax at therapeutic dose levels in both monkey and rat. All findings were determined to be non-adverse and reversible following a 28-day treatment free period. In pilot toxicity studies severe clinical signs were observed at Cmax ^{3} 18 fold and ^{3} 49 fold above the predicted Cmax at therapeutic dose levels in monkey and rat, respectively. These severe clinical signs include signs consistent with cardiovascular effects, and signs consistent with effects on the central nervous system, including tremors, pupillary changes, and decreased activity. Based on these studies, a CTA was submitted and accepted by the Netherlands Health Authority with proposed doses that enable exposures that inhibit LRRK2 up to 60% at trough in the Phase 1 clinical trial protocol and maintain margins at least 10-fold and 5-fold below the severe toxicities and the no-observed-adverse-effect-level, respectively. We believe that with the FDA mandated exposure cap for DNL201 and the protocol-defined doses for DNL151, we can achieve exposures that inhibit LRRK2 at least 50% on average over the dosing period.

Based on our robust biomarker assay capabilities to monitor target engagement and assess the exposures desired to reach our target engagement goals, the preclinical safety data support that both molecules can achieve significant levels of inhibition of LRRK2 kinase activity in the brain at dose levels that can be evaluated in clinical studies under the FDA mandated exposure cap and the protocol defined limits for DNL201 and DNL151, respectively.

Biomarker-Driven Development

We are using genetic, biochemical and imaging biomarkers to support evidence of target engagement, pathway engagement of biologic function relevant to Parkinson's disease (e.g., lysosomal biology) and effect on dopaminergic neurons as well as patient selection.

We have developed validated assays that measure pS935 and pRab10 phosphorylation as a marker of LRRK2 kinase activity to demonstrate target engagement. We are also developing techniques to further investigate the impact of LRRK2 inhibition on lysosomal function or inflammation in clinical studies, including methods to assess levels of phosphorylated Rab proteins.

Brain imaging techniques have been developed to measure deficits in dopaminergic transmission, which is closely associated with the decrease of dopaminergic neurons, a hallmark of Parkinson's disease. These techniques should allow us to monitor the potential beneficial effect of our LRRK2 product candidates on neurological function.

We are initiating efforts to recruit a targeted patient population with disease causing LRRK2 mutations including G2019S, R1441C, R1441G, I2020T and Y1699C. These mutations can be easily identified with a blood test.

Development Plan

In June 2017, we initiated a randomized, double-blind, placebo-controlled, single-center Phase 1 clinical trial in healthy young and healthy elderly subjects for DNL201 (Figure 16). The study aims to investigate the safety and tolerability of single and multiple oral doses of DNL201 and characterize the PK and PD of DNL201 in plasma and CSF. Target engagement is being assessed in blood (PBMCs) using the pS935 and pRab10 biomarkers and extrapolated to estimate target engagement in the brain. As an exploratory endpoint, candidate biomarkers in CSF are also being evaluated. The target engagement goal for the LRRK2 clinical development program is to achieve at least 50% average

target inhibition over the dosing interval in order to normalize LRRK2 kinase activity. This target engagement goal is based on data indicating that LRRK2 activity in Parkinson's patients is estimated to be almost twice that of healthy individuals.

In the ongoing, blinded Phase 1 clinical trial in healthy volunteers, we have achieved dose escalation up to single doses of 60 mg and multiple doses of up to 40 mg BID. The mean CSF/unbound plasma concentration ratio was 0.99 demonstrating that DNL201 is distributed extensively into CSF, a measure of brain drug exposure. DNL201 exposures have reached the FDA mandated exposure limit. Based on clinical safety data to date, as well as investigative preclinical toxicology data supporting monitorability of these findings, we have submitted a complete response to the FDA mandated partial clinical hold in November 2017 to request lifting the exposure cap to permit additional dose escalation to achieve higher levels of target inhibition.

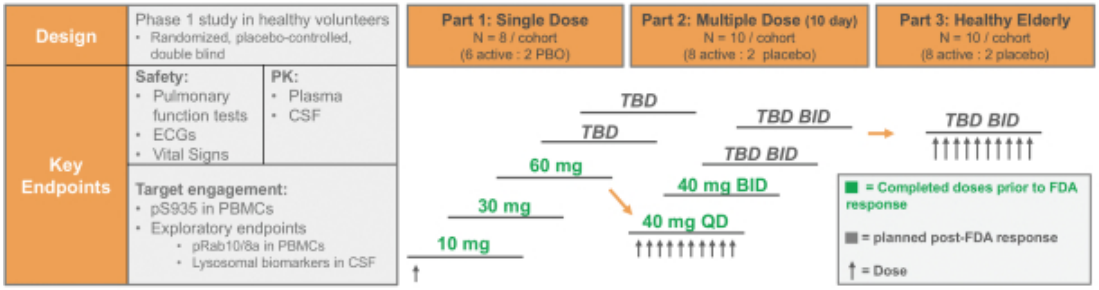


Figure 16. Overview of DNL201 Phase 1 clinical trial in healthy volunteers.

After completion of the ongoing Phase 1 clinical trial in healthy volunteers for DNL201 and the future Phase 1 clinical trial for DNL151, we plan to progress one of DNL201 or DNL151 into a 28-day Phase 1b double-blind, placebo-controlled safety, PK and biomarker study in LRRK2 mutation-carrying Parkinson's disease patients. The primary objectives of this trial will be to evaluate safety, PK and PD of such candidate in LRRK2 patients to identify the lead optimal dose(s) to study in potential future Phase 2 and Phase 3 clinical trials.

ATV:aSyn Program

Our ATV:aSyn program targets aSyn, a protein that has been identified as genetically linked to Parkinson's disease. We have developed high affinity antibodies for aSyn and are currently characterizing molecules in order to select a lead to couple with our proprietary ATV platform. We expect to file an IND or CTA for this program in 2020.

Therapeutic Rationale

aSyn is a protein in the brain linked to the development of Parkinson's disease. Lysosomal dysfunction in neurons can contribute to aSyn aggregation. This in turn leads to neuronal degeneration and results in the formation of Lewy bodies, the defining neuropathological characteristic of Parkinson's disease. Certain genetic mutations in aSyn and overexpression of the gene encoding aSyn have been identified as a cause of familial Parkinson's disease while a common polymorphism in this gene increases the risk for Parkinson's disease. Examination of human brains has revealed that aSyn pathology spreads spatially during the course of the disease, while animal model data demonstrate that this spread can be blocked with anti-aSyn antibodies (Figure 17).

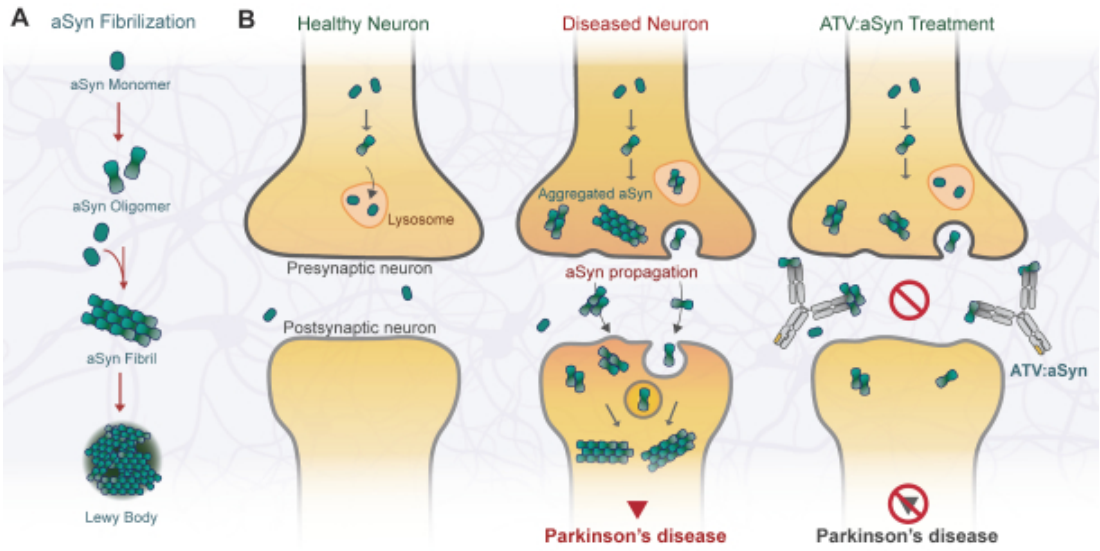


Figure 17: The aSyn protein is present in healthy neurons but can become misfolded and aggregated into oligomers, fibrils, and Lewy body pathology in Parkinson's disease (A). In diseased neurons, misfolded or oligomeric aSyn can be transmitted from one cell to another, resulting in spreading of aSyn pathology throughout the brain. ATV:aSyn antibodies are designed to block this spread through neutralizing extracellular aSyn (B).

We are developing ATV:aSyn for the treatment of Parkinson's disease. While at least one of our competitors has advanced an anti-aSyn antibody into early-stage clinical studies, we believe that ATV:aSyn will be differentiated from competitors by achieving higher brain concentrations through our ATV technology and higher affinity binding to the multiple forms of aSyn. We believe that this combination may result in superior target engagement leading to a higher probability of demonstrating efficacy in patients with Parkinson's disease.

Pharmacological Properties and Brain Exposure

We have identified a panel of anti-aSyn antibodies with different binding properties that may have best-in-class potential based on high affinity binding, distinct epitopes and excellent selectivity. We have designated three of these antibodies, anti-aSyn1, anti-aSyn2, and anti-aSyn3, as leads for further characterization. The aSyn present in the brains of Parkinson's disease patients can be found in monomer, soluble oligomer or insoluble fibril forms. Anti-aSyn1 and anti-aSyn2 display low nanomolar affinity to all forms of aSyn while anti-aSyn3 shows picomolar binding to aSyn oligomers, which have been hypothesized to represent a key toxic species in Parkinson's disease.

We determined that PK profiles for our lead anti-aSyn antibodies were comparable to a control antibody in mice. Target engagement for anti-aSyn1 and anti-aSyn2 was then demonstrated in brain using mice expressing the human form of aSyn. Both lead antibodies also demonstrated superior aSyn binding in CSF from Parkinson's disease patients as compared to benchmark anti-aSyn antibodies comparable to competitor antibodies currently in clinical development (Figure 18). This experiment establishes that both anti-aSyn1 and anti-aSyn2 bind to biologically relevant human aSyn in mice.

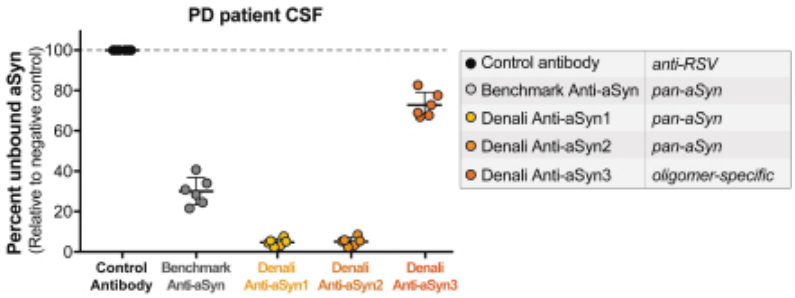


Figure 18: Our pan anti-aSyn antibodies, anti-aSyn1 and anti-aSyn2, recognize a greater proportion of extracellular aSyn present in CSF from six Parkinson's disease patients, as compared to a benchmark antibody while our oligomer-specific antibody anti-aSyn3 recognizes a smaller fraction of aSyn in CSF.

We plan to test our three lead anti-aSyn product candidates for their ability to block aSyn spreading in the brains of animal models. Our product candidate that demonstrates the most favorable profile of target engagement and efficacy will be selected for combination with our ATV platform as our first ATV:aSyn clinical candidate for IND-enabling studies. We plan to test the ability of our humanized ATV:aSyn to bind aSyn in the brain and prevent spreading of pathology using human TfR knock-in mice, as well as other experimental models.

Biomarker-Driven Development

We are focused on enabling our ATV:aSyn program via establishment of clinically translatable biomarkers of target engagement and pathway modulation. In preclinical models, we will measure levels of total aSyn and aSyn bound to antibody in the interstitial fluid of the brain, CSF and plasma to determine the level of target engagement required to block the spreading of aSyn. We plan to use these results to develop a model to identify target exposures in human required to achieve target goals for free and antibody bound aSyn in plasma and CSF that block the spread of aSyn in disease. In later stage trials, we plan to measure disease progression using imaging biomarkers (e.g. DAT imaging). We also plan to initiate work on an aSyn PET probe that would allow the extent of aSyn pathology in patient brains to be directly measured. If successful, PET imaging will be integrated into both preclinical and clinical studies to measure drug activity as well as to select patients for clinical trials.

Development Plan

Our ATV:aSyn program is currently in preclinical development, and we plan to file an IND or CTA application in 2020. Parkinson's disease will be the primary indication for this program. For our clinical studies, we plan to evaluate patients in the early stages of disease that have not yet been treated with dopaminergic replacement or dopamine agonist therapy in order to evaluate effects on function in Parkinson's disease patients. This stage of disease will also capture individuals prior to the broad spread of aSyn pathology and maximize our ability to modify the disease trajectory. Following proof of concept in Parkinson's disease, patients with other synucleinopathies, such as dementia with Lewy bodies, or DLB, and multiple system atrophy, or MSA, may also benefit and could be explored.

ETV:IDS Enzyme Replacement Therapy Program

We are developing ETV:IDS as a treatment for the lysosomal storage disorder MPS II. ETV:IDS is an IDS fusion protein that has been designed to have increased brain exposure. Lead ETV:IDS proteins are currently in preclinical development, and we plan to file an IND or CTA in the first half of 2019.

Therapeutic Rationale

MPS II, also known as Hunter Syndrome, is an X-linked recessive genetic LSD caused by a single gene defect leading to a deficiency in the enzyme IDS. IDS is essential for the breakdown of the glycosaminoglycans, or GAGs, heparan and dermatan sulfate, and its deficiency results in a toxic accumulation of these GAGs and perturbed lysosomal function (Figure 19). Clinical features of MPS II include an enlarged spleen and liver, hearing loss, respiratory tract and cardiac dysfunction, and skeletal abnormalities. Approximately two-thirds of patients suffer from the neuropathic form of the disease, which is characterized by intellectual disability and a progressive cognitive decline that emerges between three and five years of age.

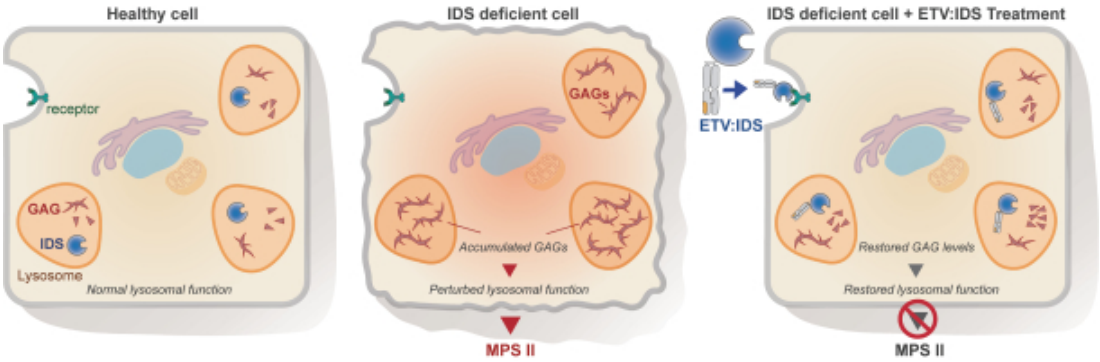


Figure 19: Lack of the lysosomal enzyme IDS results in GAG accumulation leading to lysosomal dysfunction and MPS II (Hunter Syndrome), which is characterized by a range of symptoms including neuronal degeneration. ETV:IDS is designed to promote GAG processing in the brain and reduce neuronal degeneration.

According to the MPS Society, MPS II affects between 1 in 100,000 to 1 in 150,000 males which would imply between 1,000 and 1,600 males in the United States are afflicted with MPS II based on current population estimates.

MPS II is currently treated with intravenous infusions of recombinant IDS protein. While these treatments can normalize spleen and liver size and improve walking ability, they do not efficiently distribute to the brain and, therefore, cannot address the neurological manifestations of the disease. There is a demonstrated need for therapies that effectively cross the BBB so as to treat both neurological and peripheral manifestations of MPS II and other LSDs.

Pharmacological Properties and Brain Exposure

We are developing therapeutic fusion proteins that effectively cross the BBB and diffuse to critical peripheral tissues. Our ETV platform fuses an engineered Fc, which includes a TfR binding site to improve brain uptake, with an enzyme. We have successfully generated active ETV:IDS fusion proteins that retain binding to TfR and reduce accumulation of GAGs in IDS knockout cells at sub-nanomolar concentrations, showing comparable activity to our IDS benchmark enzyme (Figure 20).

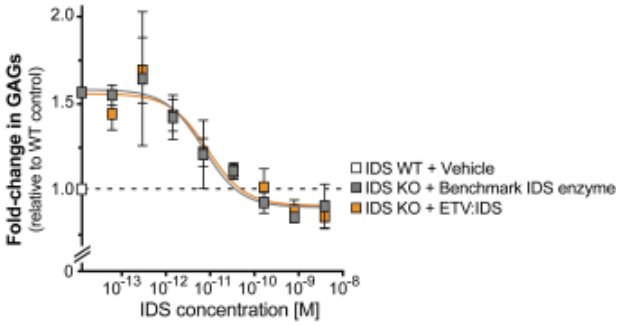


Figure 20: Measurement of ETV:IDS activity in cultured cells. Cells that do not produce the IDS enzyme (IDS KO cells) were treated with increasing doses of benchmark IDS enzyme or ETV:IDS, and the reduction in GAG accumulation was measured using LC-MS/MS. Treatment with ETV:IDS resulted in a dose-dependent reduction in GAG levels, lowering GAGs to levels seen in WT cells. ETV:IDS showed comparable cellular potency to the benchmark IDS enzyme.

We are currently analyzing the tissue distribution and efficacy of ETV:IDS fusion proteins *in vivo* using both IDS knockout mice and a proprietary human TfR knock-in mouse model. These studies are enabled by proprietary methodologies that we have developed to monitor the amount of GAG accumulation and the PK profile of intact ETV:IDS fusion proteins in these animals. Our initial studies in IDS knockout mice have shown that our lead ETV:IDS fusion protein is efficacious *in vivo*, significantly reducing GAGs in serum of mice lacking normal IDS function (Figure 21). Using our human TfR knock-in mouse model, we have also demonstrated a significant improvement in brain uptake with the ETV:IDS fusion protein, compared to an IDS-Fc control construct that does not bind TfR.

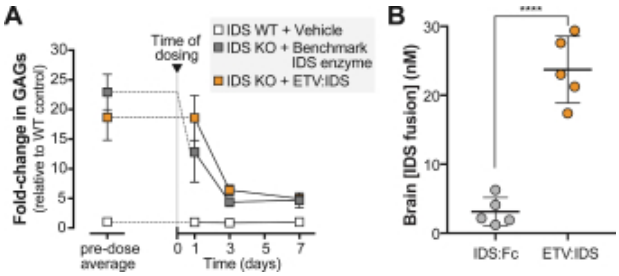


Figure 21. Measurement of the *in vivo* efficacy and brain uptake of ETV:IDS. GAG levels were measured in IDS KO mice dosed with 1mg/kg benchmark IDS enzyme, the equivalent dose of ETV:IDS (n=8), or vehicle. ETV:IDS administration reduced GAG levels in serum to levels comparable to that seen with the benchmark IDS enzyme (A). Human TfR knock-in mice were dosed with the ETV:IDS fusion or the IDS-Fc fusion control for four hours, and the concentration of IDS fusions in brain was measured using an ELISA-based assay. Significantly higher levels of the ETV:IDS fusion were detected in brain compared to the IDS-Fc control (B). ** indicates P<0.0001.**

Biomarker-Driven Development

Studies have demonstrated accumulation of GAGs in plasma and urine of MPS II patients as well as elevated levels of GAGs in CSF of both attenuated and neuronopathic MPS II patients. GAG levels have emerged as an accepted biomarker of therapeutic efficacy for treatment of MPS II and related LSDs based on positive correlations between the reduction of urine GAG levels and clinical endpoints following administration of approved therapy for MPS II. Because approved MPS II therapies are not able to cross the BBB, CSF GAG levels remain elevated in MPS II patients who are undergoing approved MPS II therapies.

We have developed a highly sensitive assay to assess levels of heparan and dermatan sulfate accumulation *in vivo* that will allow us to quantitatively investigate the PD effect of our product candidate in preclinical studies and clinical trials. This assay has shown that IDS deficiency leads to the accumulation of GAGs heparan and dermatan sulfate in tissues and fluids of IDS knock-out mice.

Development Plan

We plan to file an IND or CTA for our lead ETV:IDS product candidate in early 2019. We plan to study such product candidate in a Phase 1/2 12-week multiple-ascending dose study in MPS II patients, either in addition to IDS replacement therapy or in patients that have ceased administration of this therapy. We believe that the assessment of changes in CSF GAG levels in all patients, as well as the exploration of systemic effects such as reduction in urine and plasma GAG levels in patients not receiving IDS replacement therapy, will enable rapid confirmation of both distribution of ETV:IDS to the brain and the efficacy of our product candidates in brain and peripheral tissues.

Glial Biology Pathway Programs

RIPK1 Inhibitor Program

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 Alzheimer's disease and ALS. DNL747 is in IND-enabling preclinical studies and we plan to submit a CTA in early 2018.

Therapeutic Rationale

Aberrant glial biology characterized by neuro-immune dysfunction is a cardinal feature of the pathology of many chronic neurodegenerative diseases including Alzheimer's disease and ALS. Recent GWAS have identified that a large proportion of the genetic risk for late-onset Alzheimer's disease can be explained by genes that are expressed in microglia, the resident immune cells of the brain, implicating microglia as an important effector of neurodegeneration. Mutations in Optineurin, or OPTN, that cause ALS result in increased levels of RIPK1 activity in microglia, while two additional genes with genetic links to ALS, Tank Binding Kinase, or TBK, and TNFAIP3-interacting protein 1, or TNIP1, have been shown to regulate RIPK1 signaling in cell-based experiments.

RIPK1 is highly expressed by microglia and levels of RIPK1 activity are increased in chronic neurodegenerative disease. RIPK1 activation in microglia results in production of a number of pro-inflammatory cytokines that can cause tissue damage. Stimulation of RIPK1 signaling in cultured microglia results in production of cytokines and other pro-inflammatory factors, including Ccl2 (MCP-1), IL-1b, and IL-6, while treatment with RIPK1 inhibitors attenuates the induction of these factors (Figure 22). In Alzheimer's disease patients carrying the APOE4 allele, which is a prevalent genetic risk factor for Alzheimer's disease, common polymorphisms in IL-6R result in earlier onset of disease, demonstrating the potential importance of RIPK1 dependent IL-6 signaling pathways. Together, these data suggest increased RIPK1 function in microglia contributes to Alzheimer's disease, ALS and potentially other neurodegenerative diseases.

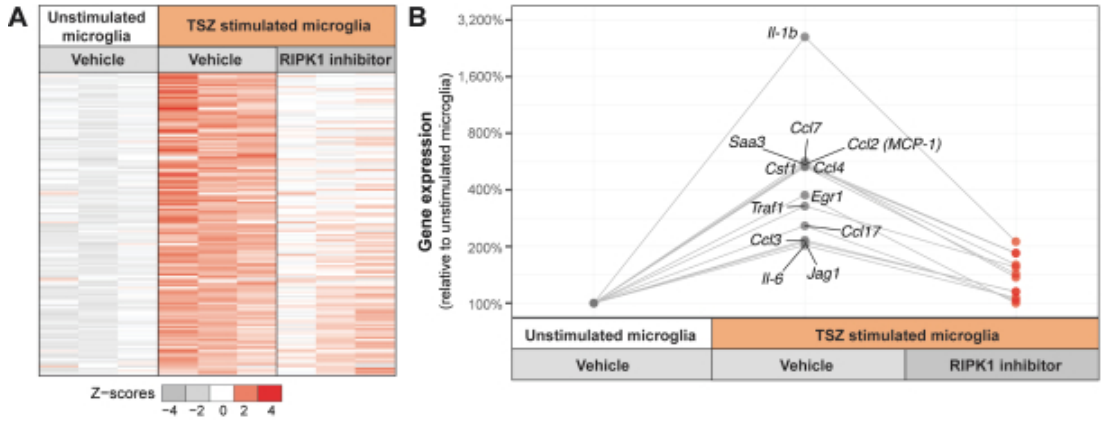


Figure 22: Production of pro-inflammatory cytokines in microglia is RIPK1 dependent. Stimulation of microglia with a TNF cocktail (TSZ) results in induction of many genes, and the majority of these changes are reversed after treatment with a RIPK1 inhibitor (A). Many of the top upregulated genes represent pro-inflammatory cytokines and chemokines such as IL-1b, IL-6 and Ccl2 (MCP-1). The up-regulation in all of these genes is reversed upon RIPK1 inhibitor treatment as shown in (B).

RIPK1 function is best characterized as being downstream of the receptor TNFR1. Specifically, the activation of RIPK1 downstream of TNFa signaling is likely a major component of the RIPK1-dependent neuro-immune phenotype observed in the context of chronic neurodegenerative disease (Figure 23). Brain penetrant inhibitors of RIPK1 therefore represent an attractive approach to targeting the TNF pathway, a highly validated biologic target in human disease, which we believe has not been adequately tested in the brain due to poor brain penetration of large molecule therapeutics, which are widely used for peripheral inflammatory disease. In addition, an oral, brain penetrant RIPK1 inhibitor could provide a more selective method to modulate TNF signaling through the pro-inflammatory TNFR1 receptor as compared to the non-selective anti-TNF antibodies that effect signaling through TNFR2, which is important for myelination of nerves, as well as TNFR1.

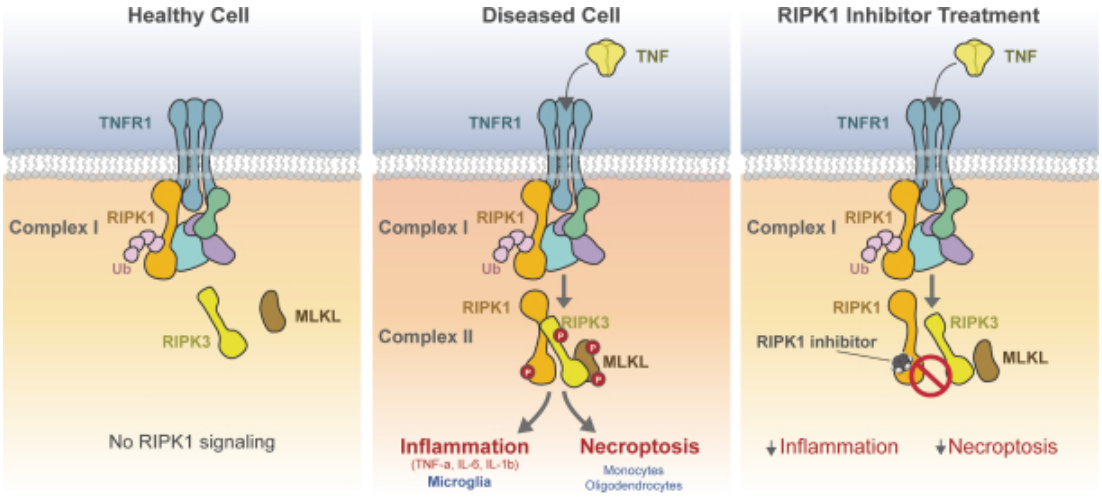


Figure 23: The RIPK1 signaling pathway displays minimal activity in healthy cells. Stimulation of TNFR1 in disease can lead to activation of RIPK1 kinase activity and generates a pro-inflammatory response in microglia and cell death via necroptosis in other cell types including monocytes and oligodendrocytes. Inhibition of RIPK1 activity with a small molecule is sufficient to block both the production of pro-inflammatory cytokines and necroptosis.

In addition to the role of RIPK1 in neuro-immune function, the RIPK1 pathway is also a central regulator of necroptosis, a form of programmed cell death. The role of RIPK1 in necroptosis of neurons has been implicated in Alzheimer's disease, providing another potential pathway where inhibition may be beneficial in disease.

We anticipate that an oral therapy targeting neuro-immune dysfunction could be used as either a monotherapy for treatment of Alzheimer's disease or in combination with therapeutics that target other mechanisms such as Tau and amyloid. Although delaying the progression of Alzheimer's disease may be most effective by targeting early stage disease (prodromal and mild Alzheimer's disease populations), we anticipate that a RIPK1 inhibitor would also have benefit in later stage Alzheimer's disease (mild to moderate Alzheimer's disease), where microglial pathology is pervasive.

Genetic risk factors identify subpopulations of the disease that may differentially respond to therapies. The neuro-immune cascade downstream of RIPK1 and the genetics of Alzheimer's disease provide candidate biomarkers for selection of a neuroinflammatory subpopulation of Alzheimer's disease that may be more responsive to a therapy targeting microglial dysfunction. These risk factors include biomarkers of neuro-immune dysfunction, such as soluble TREM2, RIPK1 dependent inflammatory cytokines in the CSF (e.g. MCP-1, IL-1b, and IL-6), and genetic risks identified by GWAS, such as the IL-6R polymorphism.

According to estimates from the Alzheimer's Association, 5.5 million people in the United States suffer from Alzheimer's disease. Approximately 4.9 million of these people have prodromal, mild and moderate Alzheimer's disease. We estimate that patients who represent a neuroinflammatory subpopulation as described above make up approximately 30% to 50% of the total patient population.

A similar approach to patient selection may be applied to ALS. According to estimates from the ALS Association, there are more than 20,000 ALS patients in the United States. Although OPTN mutations are found in only a small fraction of patients, postmortem analysis of CNS tissue reveals microglial activation and an inflammatory profile in nearly all ALS patients.

Pharmacological Properties and Brain Exposure

We have a broad portfolio of potent, selective and brain penetrant RIPK1 inhibitors with attractive pharmacological properties. The lead candidate, DNL747, is a potent, selective, orally available, brain penetrant small molecule inhibitor of RIPK1. The pharmacology of the lead has been investigated in a broad range of primary and secondary biochemical assays, cell-based *in vitro* assays, and in animals. *In vitro* studies demonstrate that DNL747 is highly selective against kinase and receptor panels. Treatment of cultured primary human microglia or macrophages with DNL747 results in a dose-dependent inhibition of RIPK1 kinase activity, as measured by reduction in pS166-RIPK1 (Figure 24A). Concentrations of DNL747 that only partially reduce pS166-RIPK1 are able to fully inhibit the production of RIPK1-dependent cytokines, such as IL-1b (Figure 24B).

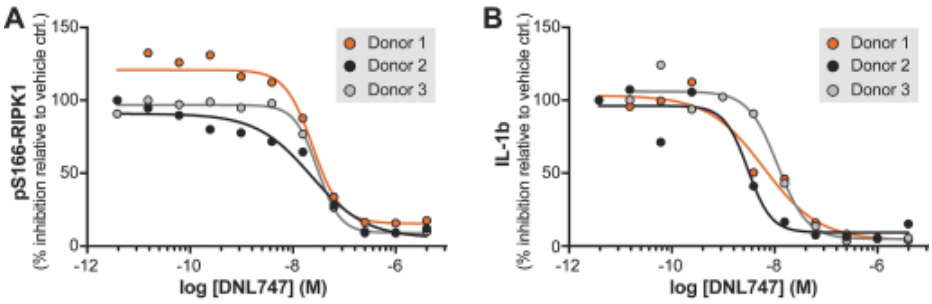


Figure 24: DNL747 demonstrates potent activity in human primary cells *in vitro*. Stimulation of primary human macrophage with a TNFa cocktail causes RIPK1 activation and production of IL-1b, while treatment with DNL747 results in a dose-dependent reduction in p-RIPK1 (A) and IL-1b production (B). Each circle represents the percent of p-RIPK1 or IL-1b relative to a control following treatment with the concentration of DNL747 denoted on the x-axis, while the lines represent curve-fits based on data from each donor throughout the range of concentrations tested. Doses evaluated in GLP toxicology studies have exposures that exceed *in vitro* concentrations showing >90% inhibition of p-RIPK1 and IL-1b.

Treatment with RIPK1 inhibitor tool compounds, including compounds we have generated, have neuro-immune modulatory effects in animal models. An increase in RIPK1 is observed both in animal models of chronic neurodegeneration and patients with Alzheimer's disease, which is correlated with microglial activation (Figure 25).

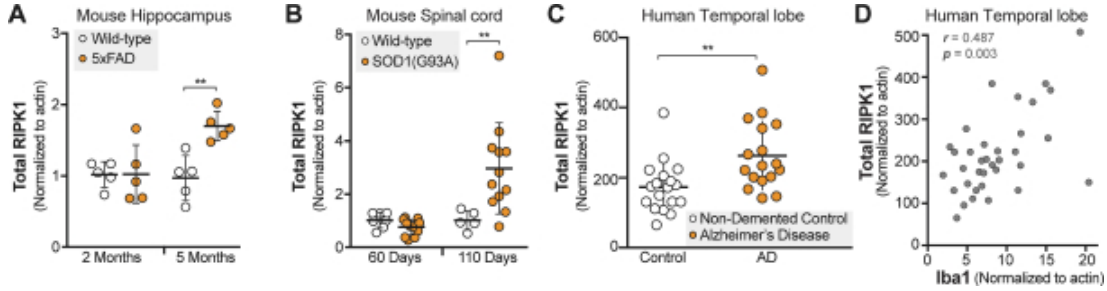


Figure 25: RIPK1 is elevated in models of chronic neurodegeneration and patients with Alzheimer's disease. An age dependent increase in RIPK1 that correlates with microglia activation can be seen in the 5XFAD model of Alzheimer's disease (A) and the SOD1 model of ALS (B). RIPK1 is also increased in the temporal lobe of patients with Alzheimer's disease (C), and this increase correlates with an elevation in the microglial marker Iba1 (D). ** indicates p<0.01.

Inhibition of RIPK1 kinase activity in animal models of neurodegeneration reduces key signatures of microglial activation and reduces levels of cytokines in the brain including soluble TREM2, IL-6 and total RIPK1 (Figure 26). Long-term treatment of Alzheimer's disease or ALS in animal models with

RIPK1 inhibitor tool compounds has been demonstrated to result in reduced neuro-immune dysfunction, attenuated neurodegeneration and improved function, as described in a recent publication in the journal *Science* by our collaborator Junying Yuan at Harvard University.

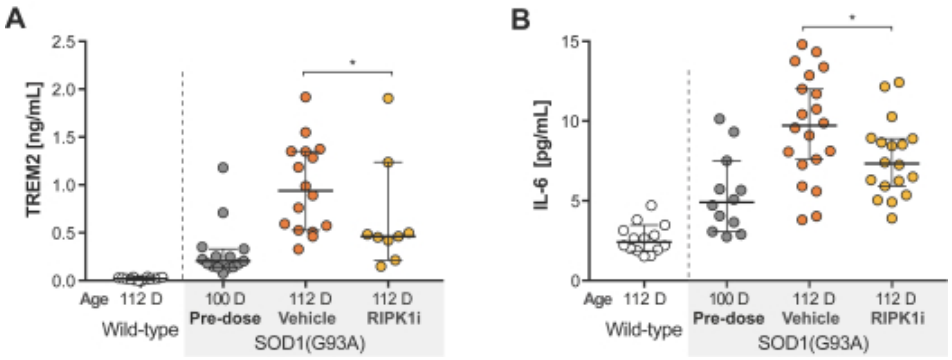


Figure 26: Short term treatment with a RIPK1 inhibitor reduces neuro-inflammatory microglial markers in neurodegenerative disease models. The SOD1 model of ALS displays elevated levels of sTREM2 and IL-6 as compared to wild type control mice at 100 days that further increases at 112 days as the disease progresses. Treatment of SOD1 mice with a RIPK1 inhibitor from 100 days of age to 112 days of age reduces levels of sTREM2 (A) and IL-6 (B) in the spinal cord to near the 100 day pre-dose levels. * indicates p<0.05.

We have completed extensive preclinical PK and PD studies with DNL747 in multiple species. Preclinical modeling of clearance predicts a human half-life compatible with twice daily dosing. PD has been characterized using a marker of RIPK1 activity, phosphorylation of RIPK1 at Serine 166, or pS166. This biomarker has been characterized in *in vitro* assays in human and monkey PBMCs and has been demonstrated to be robustly reduced by RIPK1 inhibitors.

DNL747 is currently being tested in comprehensive GLP toxicity studies, including 28-day repeat-dose studies in rat and monkey and safety pharmacology studies. DNL747 was well tolerated in pilot 7-day repeat-dose toxicity studies up to high doses and exposures. Exposures were 10- to 87-fold higher than the exposures at predicted therapeutic dose levels to achieve IC90 coverage at trough. No concerns were identified in *in vitro* safety screening for genotoxicity, cardiovascular ion channel inhibition, and hepatotoxicity assessments. We recently completed 28-day GLP safety studies in cynomolgus monkeys and rats and have reviewed preliminary data, and we expect to complete analysis of the data by the end of 2017.

Based on preliminary data from the 28-day GLP study in rat, testing at dose levels of 20 mg/kg BID to 500 mg/kg BID, it appears that DNL747 was well tolerated to the highest dose tested of 500 mg/kg BID; only minimal, non-adverse changes associated with metabolic induction were noted. Based on preliminary data from the 28-day GLP study in cynomolgus monkey, testing at dose levels of 20 mg/kg BID to 500 mg/kg BID, it appears that DNL747 was well tolerated to the mid dose of 100 mg/kg BID, with immune-mediated histopathology findings noted at the high dose of 500 mg/kg BID. Histopathology findings included lymphocytic infiltrates in the skin and/or lymphoid hyperplasia in the spleen and lymph nodes in all high dose (500 mg/kg BID) animals at terminal necropsy after the 28-day dosing phase. Clinical findings were only observed in the recovery period, two days after the last dose. One high dose animal administered 500 mg/kg BID was euthanized on Recovery Day 8 due to extensive skin lesions and histopathology findings that were more severe than, but consistent with, the other animals. One other high dose animal, which was also administered 500 mg/kg BID, had mild skin lesions and completed the recovery period. At the high dose of 500 mg/kg BID, the projected safety margins were 14- to 35-fold relative to the exposures at the predicted therapeutic dose levels to achieve IC90 coverage at trough; whereas at the mid dose of 100 mg/kg BID the projected safety

margins were 6.5- to 16-fold relative to the exposures at the predicted therapeutic dose levels to achieve IC90 coverage at trough. Because IC90 coverage at trough is expected to allow for robust inhibition of RIPK1 activity and cytokine production, we believe that these margins provide an adequate safety window to explore a robust pharmacodynamic range in humans. We believe that the preliminary data support advancing DNL747 to clinical testing with a clinical monitoring plan based on adequate safety margins in GLP toxicity studies, since we believe the projected safety margins should allow us to achieve DNL747 exposures that inhibit RIPK1 up to 90% target inhibition at trough concentrations. However, the adverse findings in the 28-day GLP study in cynomolgus monkey could result in the FDA or other regulatory authorities imposing, or us proactively proposing, an exposure cap in our planned Phase 1 clinical trial for DNL747. We intend to file a CTA with a protocol-defined maximum exposure not to exceed two fold over that which enables 90% inhibition at trough.

Biomarker-Driven Development

We have generated a number of assays to measure target engagement and pathway modulation for our RIPK1 program in order to facilitate and increase the probability of success of clinical development. To directly measure the level of RIPK1 activity, we have developed an assay to measure autophosphorylation of RIPK1 at pS166. This assay will enable quantitative measurement of target engagement in the blood of patients following a single dose or multiple doses of our RIPK1 inhibitor in Phase 1 clinical trials. Based on this information, we expect to be able to select the appropriate dose levels for later stage trials.

To measure the effect of RIPK1 on the production of pro-inflammatory cytokines by microglia, we have identified candidate pathway biomarkers of RIPK1 activity, including RIPK1 dependent cytokines, such as TNFa, IL-1b and IL-6, which are elevated in brains of patients with Alzheimer's disease. We will first use these assays to directly measure these cytokines in the CSF of subjects in a Phase 1 healthy volunteer trial to begin to determine a relationship between drug exposure and reduction of basal levels of inflammation in the brain. We then plan to use the same assays to determine the effect of RIPK1 inhibition on reduction of inflammatory cytokines in Alzheimer's disease patients and ALS patients in a small Phase 2a clinical trial. In addition to development of fluid biomarker assays, we have also invested in the development of a novel PET tracer related to a mitochondrial protein that is a biomarker of glial biology dysfunction. We are currently running a translocator protein, or TSPO, imaging study, which is a PET study in ALS patients to determine the test-retest reliability of this imaging biomarker and its utility as a direct and non-invasive measure of neuro-immune dysfunction.

In order to examine the effect of RIPK1 inhibition on the progression of neurodegeneration, we are also assessing the effect of RIPK1 inhibition in preclinical models for the effect on neurofilament (axon support) levels in blood plasma and CSF. It has recently been reported that the loss of neurons in many neurodegenerative conditions increases the levels of the protein neurofilament in both the CSF and plasma of patients. We believe that a relatively small, short clinical trial focusing on a biomarker-like neurofilament could demonstrate that a product candidate can reduce neurodegenerative processes and, therefore, build confidence in the clinical benefit of the product candidate in a larger pivotal trial.

GWAS genetic data have identified a polymorphism in the IL-6 receptor in a subset of Alzheimer's disease patients that may be a useful biomarker for selection of patients expected to benefit from RIPK1 inhibition. This common genetic variant is associated with a more prevalent neuroinflammatory phenotype in an APOE4 carrier subpopulation of Alzheimer's disease patients. As increased levels of IL-6 results from increased activity of the RIPK1 signaling pathway, patients with this IL-6 receptor mutation are expected to be more likely to respond to treatment with a RIPK1 inhibitor.

Development Plan

Pending the results from our IND-enabling preclinical studies, we plan to submit a CTA for DNL747 in early 2018 and initiate a Phase 1 clinical trial in healthy volunteers in the first half of 2018. The Phase 1 study is expected to be randomized, double-blind, placebo-controlled, single-center Phase 1 clinical trial in healthy young and elderly subjects to investigate the safety and tolerability of single and multiple oral doses of DNL747 and characterize the PK and PD of DNL747 in plasma and CSF. Target engagement will be assessed in PBMCs using the pS166 biomarker and extrapolated to estimate target engagement in brain. As an exploratory endpoint, candidate inflammatory biomarkers in the CSF are also being evaluated. We anticipate the target engagement goal for the RIPK1 clinical development program will be to achieve 70% to 90% target inhibition at trough concentrations in order to maximize inhibition of the RIPK1 pathway to enable testing of a broad range of doses in future clinical studies in patients. As an extension to our Phase 1 clinical trial design, we also plan to enroll a cohort of Alzheimer's disease patients to assess PK, safety and target engagement in this population. This will provide key insight to guide dose selection for subsequent patient trials and the identification of potential biomarker and clinical endpoints.

After completion of the Phase 1 trial in healthy volunteers, we plan to proceed to two Phase 2a studies evaluating biomarker endpoints in ALS and Alzheimer's disease. The primary objectives of these patient studies is expected to be to evaluate safety, PK and PD of DNL747 in Alzheimer's disease and ALS patients and identify evidence of central pathway engagement. We are currently evaluating endpoints to be used in these studies including CSF cytokines and TSPO imaging to demonstrate relevant effects on inflammatory cytokines and microglial function.

Back-up and Other Compounds

As part of our parallel development strategy, we have also developed a number of structurally diverse backup RIPK1 inhibitor molecules that are currently being characterized. Upon completion, we expect to be able to advance these candidates to the IND or CTA filing stage in 2019.

In August 2016, we filed a CTA for an earlier RIPK1 inhibitor compound, DNL104, and initiated a single center, randomized, double blind, placebo-controlled, dose escalating Phase 1 study in the Netherlands. Thirty-six subjects received a single dose of DNL104 and 16 subjects received multiple doses of DNL104. This study provided evidence of peripheral and CSF drug exposure and pathway inhibition by measurement of pRIPK1 in blood, and identified candidate RIPK1 dependent cytokines that change in human CSF. DNL104 was well tolerated during the dosing interval and there were no CNS related safety signals. However, three out of 16 active-treated subjects who received multiple dose developed liver test abnormalities of 2.5x to 5x above normal levels of liver enzyme activity. Based on both preclinical and clinical data, we believe that these findings are off-target liabilities that are molecule specific to the DNL104 molecule and not a result of RIPK1 inhibition. This conclusion resulted in a decision to discontinue DNL104 and advance the structurally distinct molecule DNL747, which we predict to have a superior PK profile and low risk for liver toxicity.

ATV:TREM2 Program

ATV: TREM2 is a therapeutic candidate designed to rescue microglial function in Alzheimer's disease through modulating the activity of a genetically validated target. We have developed high affinity antibodies for TREM2 and are currently characterizing molecules in order to select a lead to couple with our proprietary ATV platform. We plan to file an IND or CTA for this program in 2020.

Therapeutic Rationale

A major component of Alzheimer's disease pathology is the presence of neuro-immune dysfunction. Microglia, the resident immune cells of the brain, show signs of activation and release of

toxic cytokines in patients with Alzheimer's disease. Recent human genetic studies have identified single nucleotide polymorphism in a number of microglia specific genes that contribute to Alzheimer's disease, which strongly implicates glial function as a contributor to disease risk. TREM2 is a cell surface receptor expressed exclusively by microglia in the brain which regulates multiple processes including survival, migration, phagocytosis, and cytokine release (Figure 27). In 2013, a rare variant of TREM2 was found to be associated with a three-fold higher risk of Alzheimer's disease onset, which strongly implicates TREM2 as a functional contributor to disease progression.

The TREM2 mutations identified in patients with Alzheimer's disease results in loss of normal TREM2 function. Mouse models of Alzheimer's disease display more severe phenotypes in the absence of TREM2, including more diffuse amyloid plaques and increased synaptic loss. Conversely, data from our TREM2 expressing myeloid cell-based assays demonstrate that increasing TREM2 signaling can improve cellular survival and function, indicating that activating TREM2 has a beneficial effect on this cell type (Figure 29). Based on this combination of genetic and functional data, we hypothesize that positive modulation of TREM2 activity will improve microglia function and slow the progression of Alzheimer's disease.

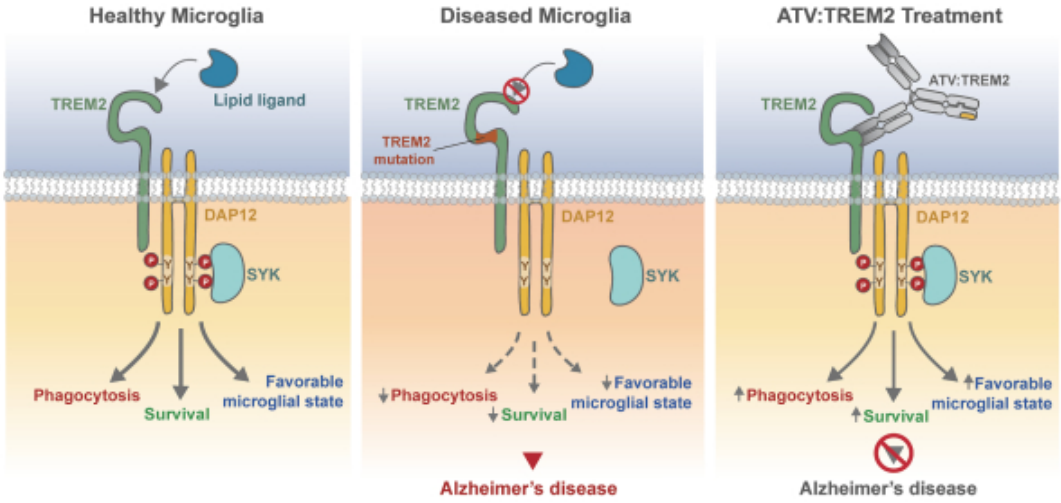


Figure 27: TREM2 is a cell surface receptor expressed on microglia. Activation of the TREM2 signaling pathway in healthy microglia leads to improved survival and promotes a favorable microglial state. TREM2 mutations result in reduced signaling and attenuated microglia function, while treatment with ATV:TREM2 is designed to improve survival and boost microglial function.

We believe that patients with a specific neuroinflammatory signature as a result of glial dysfunction may particularly benefit from therapeutics targeting positive modulation of TREM2. These patients could be identified through a combination of genetic, CSF and imaging biomarkers. This population could be expanded to encompass all prodromal to mild and moderate Alzheimer's disease patients based on a demonstration of pathway modulation in the clinic.

Pharmacological Properties and Brain Exposure

We have generated multiple classes of anti-TREM2 antibodies with affinities less than 10nM. By using an array of functional assays, we have demonstrated that these antibodies have diverse functional effects, including several that show agonism, antagonism and positive allosteric modulation (Figure 28).

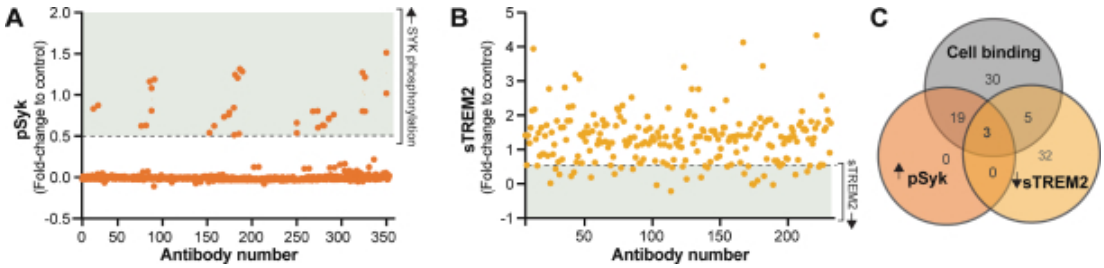


Figure 28: Profiling of our anti-TREM2 antibodies. Antibodies were profiled for their ability to induce TREM2 signaling and measured by pSyk (A) and for their effect on shedding of soluble TREM2 (sTREM2) from the cell surface (B). Anti-TREM2 antibodies were identified with various combinations of activities. This includes 57 antibodies that bound TREM2 on the surface of cells (Cell binding), of which 19 increased Syk phosphorylation (pSyk), 5 lowered soluble TREM2 levels (sTREM2), and 3 antibodies displayed both of these activities (C).

We have demonstrated that select antibodies with TREM2 agonist activity are able to improve the survival of cultured human macrophage (Figure 29). These data indicate that increasing TREM2 function can have a beneficial effect on myeloid linage cells. We are currently testing these and other anti-TREM2 antibodies in additional assays to determine which mechanism of action results in the desired effect on TREM2-mediated microglial function. We intend to then progress a lead antibody with a favorable affinity and activity profile to *in vivo* studies.

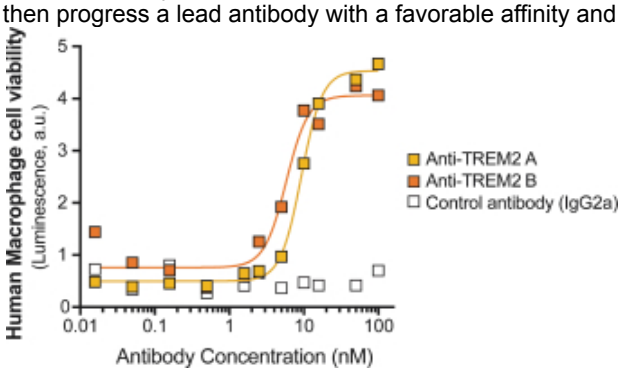


Figure 29: Our anti-TREM2 antibodies improve survival of cultured human macrophage. Treatment of primary human macrophage with anti-TREM2A and anti-TREM2B is sufficient to increase survival in a dose-dependent fashion.

We will evaluate the lead TREM2 antibodies *in vivo* for target engagement and disease-relevant efficacy in animal models of Alzheimer's disease. We will then progress the most promising of the lead TREM2 antibodies as a potential clinical candidate to be humanized and coupled with our ATV platform, ATV:TREM2, in order to improve brain uptake and enable target engagement in clinical studies.

Biomarker-Driven Development

The development of ATV:TREM2 is expected to be facilitated by a number of biomarkers to measure target engagement, pathway modulation and impact on disease progression. Upon cleavage of the extracellular domain of TREM2, a soluble form of TREM2, sTREM2, is released from the cell surface. sTREM2 is detectable in CSF. We have focused on anti-TREM2 antibodies that modulate the levels of sTREM2, enabling sTREM2 to be used as a biomarker of target engagement both in preclinical models and Phase 1 clinical trials. We intend to correlate TREM2 levels with downstream functional endpoints using preclinical models, allowing measurement of sTREM2 levels in a Phase 1 clinical trial to confirm target engagement and increase the probability of success.

The ability of ATV:TREM2 to modulate microglial function in preclinical models will be measured through histology and examination of microglial gene expression. These endpoints will be correlated to readouts that can be measured in clinical studies such TSPO-PET imaging and cytokine levels in CSF. As part of clinical trials, we plan to examine these endpoints both pre-dose and following treatment to assess microglia activation state.

Development Plan

The primary indication for ATV:TREM2 is Alzheimer's disease. The development of ATV:TREM2 will be facilitated by a number of biomarkers to measure target engagement, pathway modulation and an impact on disease progression. Our focus on anti-TREM2 antibodies that modulate levels of sTREM2, a soluble form of TREM2, will enable sTREM2 to be used as a biomarker of target engagement both in preclinical models and Phase 1 clinical trials. sTREM2 is released from the cell surface upon cleavage of the extracellular domain of TREM2 and is detectable in CSF. In preclinical models dosed with ATV: TREM2, sTREM2 levels will be correlated with the ability of ATV:TREM2 to modulate microglial function as assessed through histology and examination of microglial gene expression. Understanding the relationship between changes in sTREM2 and microglial function, will enable assessment of both target engagement and a biologically relevant effect of ATV:TREM2 dosing in Phase 1 clinical trials. Early stage clinical studies will also assess candidate biomarkers to identify patients that are most likely to benefit from a TREM2 mediated approach. Examples of these candidate biomarkers include CSF sTREM2 and TSPO-PET, two biomarkers that are elevated in patients with Alzheimer's disease. These examples may be used as both a patient selection biomarker to identify patients with pathologic neuro-immune function and as a measure of TREM2 pathway modulation.

These endpoints will be correlated to readouts that can be measured in clinical studies such TSPO-PET imaging and cytokine levels in CSF. As part of clinical trials, we plan to examine these endpoints both pre-dose and following treatment to assess microglia activation state. We plan to file an IND or CTA for this program in 2020.

Cellular Homeostasis Pathway Program

ATV: BACE1/Tau Program

ATV: BACE1/Tau is a bispecific program targeting the production of amyloid beta, or Abeta, and the spreading of Tau, the two key pathological processes of Alzheimer's disease. We have developed high affinity antibodies for BACE1 and Tau and are currently optimizing them before combining them into a single therapeutic agent using our proprietary ATV platform. We plan to file an IND or CTA in 2020.

Therapeutic Rationale

Alzheimer's disease pathology is characterized by the presence of amyloid plaques and neurofibrillary tangles. The pathologies arise as a consequence of protein aggregation, a form of disrupted cellular homeostasis, eventually leading to neuronal degeneration. Amyloid plaques are comprised of Abeta, an extracellular fragment of amyloid precursor protein, or APP, which is generated by cleavage of APP by BACE1 and gamma secretase. Mutations in APP processing components that increase Abeta levels are sufficient to cause early onset Alzheimer's disease. Conversely, mutations in APP that reduce BACE1 cleavage may protect individuals from Alzheimer's disease. These genetic links demonstrate the central role of the amyloid pathway in Alzheimer's disease, and are particularly supportive of BACE1 inhibition as a therapeutic approach (Figure 30).

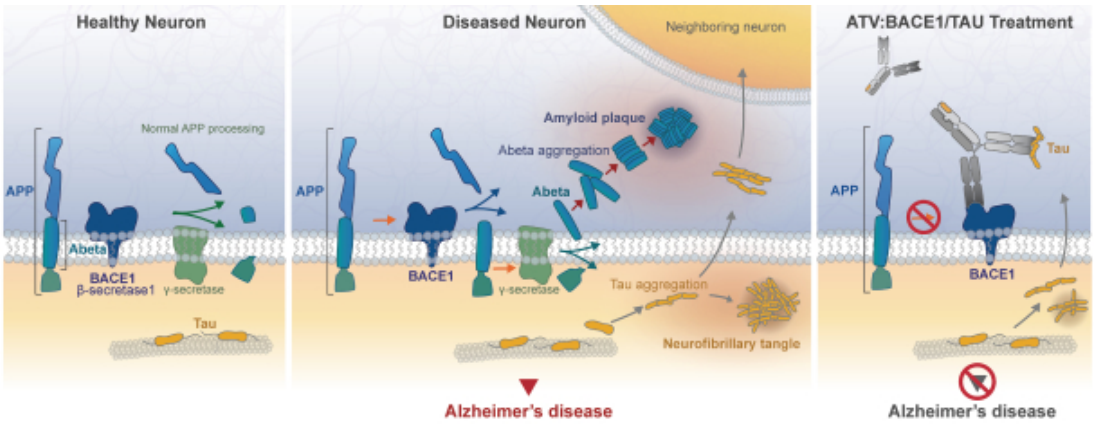


Figure 30: Abeta is generated through sequential cleavage of APP by beta-secretase 1 (BACE1) and gamma secretase to generate Abeta. In Alzheimer's disease, Abeta aggregates to form oligomers and amyloid plaques. Tau is present in healthy neurons but can misfold and aggregate in disease to form either neurofibrillary tangles or Tau oligomers that can spread from one cell to another in disease. ATV:BACE1/Tau is designed to block both of these Alzheimer's disease pathologies through inhibiting cleavage of APP by BACE1 and sequestering extracellular Tau to prevent its spread.

Tau is believed to regulate microtubule stability in neurons, but it can also aggregate to form neurofibrillary tangles present in many neurodegenerative diseases, including Alzheimer's disease. Detailed examination of Alzheimer's disease patients' brains has revealed that Tau pathology spreads spatially during the course of the disease. This spreading of Tau pathology is correlated with cognitive decline. Tau antibodies are currently in clinical development based on animal model data demonstrating that they are capable of blocking the spread of Tau pathology.

Preclinical data also show amyloid pathology accelerates Tau pathological spreading, which is consistent with findings in Alzheimer's disease patients that show Tau pathology progresses later as compared to amyloid plaques. Therefore, our approach of targeting both pathologies with a bispecific antibody may also have synergistic activity. The target patient population for our ATV:BACE1/Tau clinical studies is patients with early-stage Alzheimer's disease and confirmed Abeta pathology as measured by amyloid PET imaging.

Pharmacological Properties and Brain Exposure

We have discovered lead anti-BACE1 and anti-Tau antibodies that have been humanized and are now undergoing optimization processes designed to further improve affinity and cellular potency. Our anti-BACE1 lead displays less than 10nM cellular potency for inhibition of Abeta production (Figure 31). We have also identified a backup anti-BACE1 antibody with improved inhibition of BACE1 that is currently undergoing affinity maturation. Anti-BACE1 antibodies have demonstrated improved selectivity as compared to small molecule approaches currently in clinical development by sparing inhibition of BACE2, which has the potential to lead to a superior safety profile following chronic dosing. When coupled to our ATV platform, anti-BACE1 antibodies have been shown to reduce Abeta levels in the brain by approximately 55% in a human TfR mouse model.

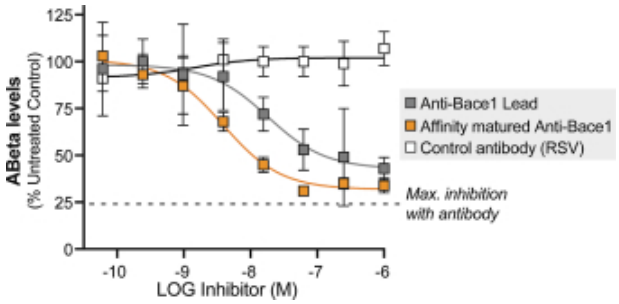


Figure 31: Activity of our anti-BACE1 antibodies. Our lead anti-BACE1 antibody and an affinity matured humanized version of anti-BACE1, are each able to inhibit Abeta production by cells. The affinity-matured humanized anti-BACE1 antibody demonstrates improved potency as compared to the parent anti-BACE1 antibody.

Our lead anti-Tau antibody recognizes all forms of Tau present in the brains of Alzheimer's disease patients and has high affinity. It demonstrates superior target engagement in animal models as compared to our benchmark antibodies which are similar to certain antibodies that third parties currently have in clinical development, even without being coupled to our ATV platform (Figure 32). We believe the epitope recognized by our Tau antibody is advantageous relative to binding sites of benchmark antibodies as it would recognize truncated forms of Tau not recognized by antibodies directed against N-terminal or C-terminal epitopes.

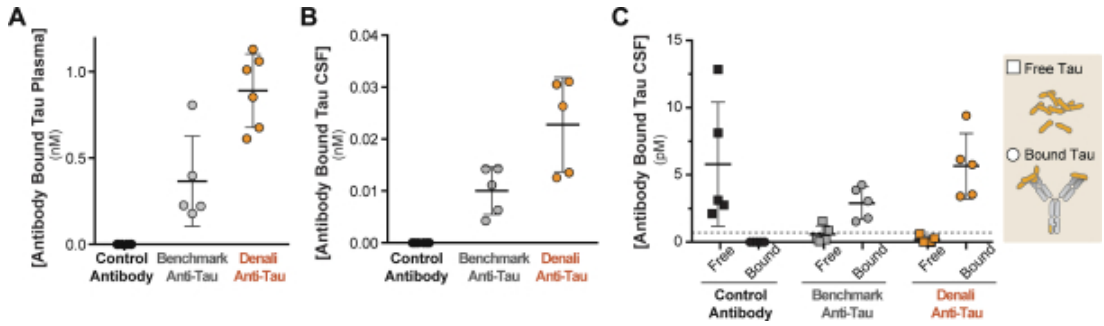


Figure 32. Our lead anti-Tau antibody displays target engagement that is superior to benchmark antibodies. The amount of antibody bound Tau in either plasma (A) or CSF (B) following a single dose of our lead anti-Tau antibody, a benchmark anti-Tau antibody or a control anti-Tau antibody. Our lead anti-Tau also recognizes a significant portion of the extracellular Tau present in Alzheimer's patient CSF (C).

We have conducted proof of concept studies with anti-BACE1/Tau bispecific antibodies that demonstrate both arms retain full functionality when combined into a single molecule as measured by a reduction of Abeta in cellular assays and blocking of Tau seeding in cells.

We believe our ATV:BACE1/Tau program may be the first therapeutic to target both hallmark Alzheimer's disease pathologies as a single therapeutic agent and has the potential for synergistic activity, restoring protein homeostasis with regards to the two most common Alzheimer's disease pathologies. To directly demonstrate the efficacy of the ATV:BACE1/Tau molecule, we are developing a proprietary mouse model by crossing our human TfR knock-in mouse with an established genetic model of Tau pathology. These preclinical efficacy studies are planned for 2018, and are expected to enable the examination of brain exposure and Abeta levels in the brain, and assess the effect on spreading of Tau pathology.

Biomarker-Driven Development

We plan to use validated genetic, biochemical and imaging biomarkers to support patient selection, evidence of target engagement and functional efficacy for our ATV:BACE1/Tau program. These include assays for measurement of CSF Abeta and Tau, as well as Abeta and Tau PET imaging tracers. The acute measurement of Abeta after BACE1 inhibition can be utilized to confirm ATV:BACE1/Tau uptake and target engagement, thus validating our ATV platform for BBB uptake in humans in Phase 1 clinical testing.

In preclinical models, brain levels of Abeta are reduced following a single dose of a BACE1 antibody coupled to the ATV platform (Figure 5), while dosing Tau antibodies led to increased levels of Tau bound to antibody in plasma and CSF. These two readouts can be translated to human testing by measuring CSF levels as a direct measure of target engagement for an ATV:BACE1/Tau molecule. Preclinical studies will be conducted to measure CSF levels of Abeta and Tau in animal models and correlated to effects on amyloid and Tau pathology following chronic dosing. These data and established CSF biomarkers are expected to enable effective testing of ATV:BACE1/Tau in humans.

Development Plan

Our Phase 1 clinical trials will be designed to evaluate the safety and pharmacology of ATV:BACE1/Tau and evaluate target engagement in both healthy volunteers and Alzheimer's disease patients. In this study and in later stage clinical trials, we plan to measure the activity of ATV:BACE1/Tau through CSF Abeta measurement, confirming BACE1 inhibition. In later stage clinical studies we plan to use Tau PET imaging to ascertain whether ATV:BACE1/Tau is able to prevent the spread of Tau pathology. Our target patient population is patients with prodromal and mild Alzheimer's disease and confirmed Abeta pathology as measured by amyloid PET imaging. We estimate this patient population to be approximately 3.4 million in the United States.

The results from this Phase 1 study with ATV:BACE1/Tau will provide information on the overall safety and pharmacologic profile of our ATV platform.

Back-up and Other Compounds

We are also pursuing ATV:Tau bivalent as an alternative approach to ATV:BACE1/Tau. This molecule will have the added advantage of two antibody arms engaging Tau, resulting in potentially higher affinity target engagement, combined with ATV to improve brain exposure. This approach is attractive as local target concentrations of Tau in the synapse may be high. A decision to advance ATV:Tau will be based on establishing superior target engagement biomarker data in animal model CSF and human CSF as compared to known competitor molecules. We plan to file an IND or CTA in 2020.

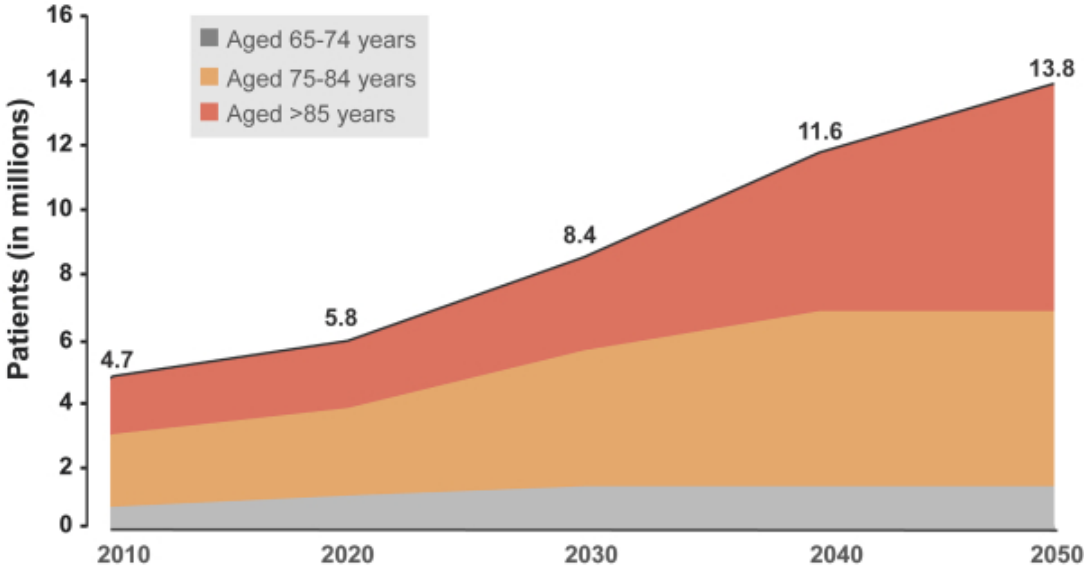
Neurodegeneration: A Significant Unmet Medical Need

Neurodegeneration is one of the largest unmet medical needs of our time, with a rapidly growing patient population. The risk of most neurodegenerative diseases increases with age, but people of all ages can also be affected due to genetic and/or environmental factors. Neurodegenerative diseases are generally progressive in nature and result in the degeneration and/or death of neurons in the brain that result in cognitive decline, functional impairment and eventually death. Alzheimer's and Parkinson's diseases represent the largest among the neurodegenerative diseases.

There are few effective therapeutic options available for patients with Alzheimer's disease, Parkinson's disease, ALS and other neurodegenerative diseases.

Alzheimer's Disease

Alzheimer's disease is a progressive form of dementia that impacts cognitive and motor function in those with the disease. Alzheimer's disease is likely a heterogenous disease driven by genetic risk and environmental factors with common pathology of amyloid deposition in the brain. It is estimated by the World Health Organization to represent between 60% to 70% of all cases of dementia. Alzheimer's disease is the sixth leading cause of death in the United States. As the disease progresses, patients lose the ability to carry out basic daily tasks and eventually to respond to their environment. According to estimates from the Alzheimer's Association, 5.5 million people in the United States suffer from Alzheimer's disease, and patient prevalence is expected to increase to 13.8 million people by 2050.



Source: Alzheimer's Association
Figure 33: Projected number of people in the United States with Alzheimer's disease.

The cost of care to society is massive. The direct costs of caring for individuals with Alzheimer's disease and other dementias in the United States will total an estimated $259 billion in 2017, and is projected to increase to $1.1 trillion by 2050, according to the Alzheimer's Association.

The two classes of drugs approved for the treatment of Alzheimer's disease dementia are cholinesterase inhibitors (donepezil, galantamine, rivastigmine and tacrine) and NMDA receptor antagonists (memantine). These therapeutic products do not modify or alter the progression of the underlying disease and provide only modest efficacy in treating the symptoms of Alzheimer's disease. Namenda (memantine), the most recent FDA-approved new therapeutic product for Alzheimer's disease, was approved in the United States in 2003.

Parkinson's Disease

Parkinson's disease is the second most common neurodegenerative disease of adult onset, behind only Alzheimer's disease. Parkinson's disease is a chronic and progressive movement disorder. According to the Parkinson's Disease Foundation, as many as one million people in the United States today suffer from Parkinson's disease, with approximately 60,000 Americans diagnosed with Parkinson's disease each year.

Lysosomal dysfunction is a central pathology of Parkinson's disease. Certain genetic mutations affecting lysosomal dysfunction, such as LRRK2, aSyn and GBA mutations, are linked to Parkinson's disease. In addition, clinical diagnosis of Parkinson's disease without a known cause is called idiopathic Parkinson's disease and represents the majority of known cases.

For Parkinson's disease, most therapeutic products approved for treatment of the motor symptoms of the disease are related to levodopa and other dopamine agonists. While some existing products provide meaningful symptomatic relief, they have significant side effect risks, fail to address the progression of the disease, and over time gradually lose their effectiveness in treating the symptoms of the disease.

Other Rare Neurodegenerative Diseases

There are many types of rare neurodegenerative diseases, including ALS and LSDs, among others. ALS is a severe and fast progressing neurodegenerative disease. The incidence rate of ALS in the United States is approximately 2 in 100,000 people, with more than 20,000 people in the United States currently suffering from ALS, according to estimates from the ALS Association. The life expectancy of a patient with ALS averages two to five years after diagnosis. By 2040, the projected number of ALS cases in the United States is expected to increase to approximately 30,000.

LSDs are a group of approximately 50 inherited metabolic diseases that are characterized by an abnormal build-up of various toxic materials in the body's cells. LSDs are usually triggered when a particular enzyme is missing or exists in too small an amount to enable the complete breakdown of macromolecules. Each LSD is characterized by the nature of the substances that accumulate and their effects on the body. As a group, LSDs have an estimated frequency of about one in every 5,000 live births. Some of the most common LSDs are Gaucher disease, Fabry disease, and MPS II (Hunter Syndrome). Other rare neurodegenerative indications include Huntington's disease, frontotemporal dementia and spinal muscular atrophy, among others.

Manufacturing

We believe it is important to our business and success to have a reliable, high-quality preclinical and clinical drug supply. As we mature as a company and approach commercial stage operations, securing reliable high-quality commercial drug supply will be critical.

We do not currently own or operate facilities for product manufacturing, storage, distribution or testing.

We rely on third-party contract manufacturers, or CMOs, to manufacture and supply our preclinical and clinical materials to be used during the development of our product candidates. We have established relationships with several CMOs, including Lonza Sales AG, or Lonza, as described below.

We currently do not need commercial manufacturing capacity. When and if this becomes relevant, we intend to evaluate both third-party manufacturers as well as building out internal capabilities and capacity. We may choose one or both options, or a combination of the two.

Effective September 2017, we entered into a development and manufacturing services agreement with Lonza, which agreement we amended in October 2017 to add the initial scope of work under this agreement. We refer to this agreement, as amended, as the DMSA or the Lonza agreement. Pursuant to the Lonza agreement, Lonza agreed to provide clinical development and manufacturing services with respect to certain of our biologic products on a fee-for-service basis. In addition, as long as we are not in breach of the Lonza agreement and Lonza has not terminated the Lonza agreement for our

material breach or insolvency, we have the right to transfer the manufacturing process for our products to ourselves or a third party designated by us and approved by Lonza, subject to payment of a reasonable royalty or licensing fee and terms to be negotiated.

Under the Lonza agreement, Lonza has a right of first refusal to exclusively manufacture a certain number of our biologic products produced in mammalian expression systems that we progress into clinical development for neurodegenerative indications. We refer to these products as pipeline products. If Lonza does not exercise its right of first refusal to manufacture a particular pipeline product, we will be free to utilize a third party manufacturer for such product. Lonza's right of first refusal will not apply with respect to any pipeline product if we enter into a bona fide partnership with a third party (other than a CMO) with respect to such product and such partner will perform development or manufacturing services with respect to such product. We retain the right to conduct any in-house development and manufacturing activities with respect to pipeline products.

If we elect to use Lonza's proprietary expression system in the manufacture of a product, we are required to negotiate a license with Lonza to use such system prior to *in vivo* clinical studies or commercial use or sale of such product. Pursuant to such license, we will be required to pay annual license fees on a product-by-product basis if (i) we (or our strategic partner) and Lonza both manufacture a particular product using such system and we do not guarantee Lonza a certain high double digit percentage of our production requirements of such product, or (ii) if we utilize a third party CMO to manufacture a product using such system. However, we will not be required to pay any annual license fee for any product produced using such system if (i) Lonza is the sole manufacturer of such product or if (ii) we and Lonza both manufacture such product and we guarantee Lonza a certain high double-digit percentage of our production requirements of such product.

Except for products for which Lonza is the sole manufacturer, we will also be required under this license to pay royalties in a range up to a maximum in the low single-digit percentages on net sales of each product produced using such system. Our royalty payment obligations will expire on a country-by-country and product-by-product basis upon the later of (i) the expiration of the last valid licensed patent claim covering such product in such country or (ii) ten years after the first commercial sale of such product in such country.

Unless earlier terminated, the Lonza agreement will expire on September 6, 2022. Lonza may terminate the Lonza agreement for convenience with 24 months' notice and Lonza may terminate the Lonza agreement if we assign the Lonza agreement to one of our affiliates or a third party or undergo certain change of control transactions and the assignee or acquirer is (i) a competing contract manufacturing organization, (ii) located outside of the European Union or United States, or (iii) an entity about which Lonza has bona fide concerns. We may terminate the Lonza agreement for convenience with 12 months' notice. Finally, either we or Lonza may terminate a particular project in the event the services required to complete such project cannot be completed following a specified notice and resolution period.

Except in the event we terminate the Lonza agreement for Lonza's material breach, in addition to other termination-related fees, we will be obligated to pay Lonza all or a portion of the amounts payable for any cancelled services, depending on how far in advance of the start of such services we terminate the agreement.

Commercialization Plan

We do not currently have any approved drugs and we do not expect to have any approved drugs in the near term. Therefore, we have no sales, marketing or commercial product distribution capabilities and have no experience as a company in marketing drugs.

When and if any of our product candidates are approved for commercialization, we intend to develop a commercialization infrastructure for those products in the United States and potentially in certain other key markets. We may also rely on partnerships to provide commercialization infrastructure, including sales and marketing and commercial distribution.

Competition

The biotechnology and pharmaceutical industries, including in the neurodegenerative disease field, are characterized by rapidly advancing technologies, strong competition and an emphasis on intellectual property. We face substantial competition from many different sources, including large and specialty pharmaceutical and biotechnology companies, academic research institutions, governmental agencies and public and private research institutions. We believe that the key competitive factors affecting the success of any of our product candidates will include efficacy, safety profile, method of administration, cost, level of promotional activity and intellectual property protection.

Our product candidates will compete with current therapies approved for the treatment of neurodegenerative diseases, which to date have been primarily targeted at treating the symptoms of such diseases rather than halting or slowing the progression of the disease. However, in addition to such currently approved therapies, we believe that our product candidates, if approved, may also compete with other potential therapies intended to halt or slow the progression of neurodegenerative disease that are being developed by a number of companies and institutions, including but not limited to:

- *Alzheimer's Disease*: Potentially disease modifying therapeutics are being developed by several large and specialty pharmaceutical and biotechnology companies, including Biogen, Eli Lilly, Eisai, GlaxoSmithKline, Merck and Roche (including Genentech, its wholly owned subsidiary), and are in various stages of clinical trials.
- *Parkinson's Disease*: Potentially disease modifying therapeutics are being developed by several large and specialty pharmaceutical and biotechnology companies, including Prothena, Roche, Sage Therapeutics and Sanofi, and are in various stages of clinical trials.
- *ALS:* Potentially disease modifying therapeutics are being developed by several large and specialty pharmaceutical and biotechnology companies and academic institutions, including Cytokinetics and Mallinckrodt, and are in various stages of clinical trials.
- *Lysosomal Storage Diseases*: The currently approved treatments for LSDs are enzyme based therapies. Potentially disease modifying therapeutics are being developed by several large and specialty pharmaceutical and biotechnology companies, including ArmaGen, BioMarin, JCR Pharmaceuticals, Sanofi, Shire and Ultragenyx, and are in various stages of clinical trials.

In addition, there are companies that are developing technologies that would compete directly with our technologies, including:

- *Blood-Brain Barrier Technology*: There are several large and specialty pharmaceutical and biotechnology companies developing BBB delivery technologies that utilize RMT, including AbbVie, biOasis Technologies, ArmaGen, JCR Pharmaceuticals and Roche (including Genentech, its wholly owned subsidiary), among others.

Intellectual Property

Our intellectual property is critical to our business and we strive to protect it, including by obtaining and maintaining patent protection in the United States and internationally for our product candidates,

novel biological discoveries and BBB platform technology, including new targets and applications, and other inventions that are important to our business. We also rely on trademarks, trade secrets, know-how, continuing technological innovation and licensing opportunities to develop and maintain our proprietary position.

For our product candidates, we generally pursue patent protection covering compositions of matter, methods of use and manufacture. For example, our most advanced product candidate in the LRRK2 program, DNL201, is covered by an issued composition of matter patent in the United States and several other countries. Furthermore, we own and have filed patent applications in the United States that are directed to the composition of matter of certain antibodies and small molecule product candidates that we intend to develop, as well as the Fc domain portion of our BBB platform technology that binds to TfR. However, 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. 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, or issued patents in the United States directed to the composition of the Fc domain portion of our BBB platform technology that binds to TfR, or issued patents in the United States directed to the composition of the specific product candidates being developed in our TREM2, aSyn or IDS core programs. As further described below, we have filed or intend to file patent applications on these and other aspects of our technology and product candidates, and as we continue the development of our product candidates, we intend to identify additional means of obtaining patent protection that would potentially enhance commercial success, including protection for additional methods of use, formulation or manufacture.

ATV/ETV Programs

For our ATV programs, we license multiple patent families from F-star directed to, among other things, modifying immunoglobulin non-CDR loops to create antigen binding sites. These licensed patent families include approximately four issued U.S. patents and five pending U.S. non-provisional patent applications, and over 180 issued foreign patents and over 10 pending foreign patent applications, with pending or issued claims related to the modification process for, and in one issued European patent, the composition of, the modified immunoglobulin non-CDR loops. The issued patents in the earliest of these families are expected to expire in 2026, not including any patent term adjustments and any patent term extensions.

Furthermore, we own three pending U.S. provisional applications directed to the composition and sequences of our TfR-binding ATVs. Any future U.S. and foreign patents that may issue from these patent families (assuming the necessary non-provisional patent applications are timely filed and all other applicable requirements are satisfied) would be expected to expire in 2038, excluding any patent term adjustments and any patent term extensions. We do not own or in-license any issued U.S. patents that are directed to the composition of matter of our ATV programs.

ATV: BACE1/Tau

In addition, we license one patent family from VIB that is directed to, among other things, our anti-BACE1 antibody to be used with our BBB platform technology licensed from F-star. This licensed family includes one issued U.S. patent and one pending U.S. non-provisional patent application; and approximately 16 issued foreign patents and three pending foreign patent applications, with pending or issued claims related to composition of hybridomas, their active fragments and key epitopes. The issued patents in this family are expected to expire in 2030, excluding any patent term adjustments and any patent term extensions. Furthermore, we own one pending U.S. provisional application directed to additional anti-BACE1 antibodies of ours for use with our BBB platform technology licensed from F-star. Any future U.S. and foreign patents that may issue from this patent family (assuming the

necessary non-provisional patent applications are timely filed and all other applicable requirements are satisfied) would be expected to expire in 2038, excluding any patent term adjustments and any patent term extensions. We own two pending U.S. provisional applications directed to, among other things, our anti-Tau antibody to be used with our BBB platform technology licensed from F-star. Any future U.S. and foreign patents that may issue from this patent family (assuming the necessary non-provisional patent applications are timely filed and all other applicable requirements are satisfied) would be expected to expire in 2038, excluding any patent term adjustments and any patent term extensions. We also own one pending U.S. provisional application directed to, among other things, anti-BACE1/anti-Tau bispecific antibodies for use with our BBB platform technology licensed from F-star. Any future U.S. and foreign patents that may issue from this patent family (assuming the necessary non-provisional patent applications are timely filed and all other applicable requirements are satisfied) would be expected to expire in 2038, excluding any patent term adjustments and any patent term extensions.

ATV: aSyn

We own two pending U.S. provisional applications directed to, among other things, our anti-aSyn antibodies to be used with our BBB platform technology licensed from F-star. Any future U.S. and foreign patents that may issue from this patent family (assuming the necessary non-provisional patent applications are timely filed and all other applicable requirements are satisfied) would be expected to expire in 2038, excluding any patent term adjustments and any patent term extensions.

ATV: TREM2

We own two pending U.S. provisional applications directed to, among other things, our anti-TREM2 antibodies to be used with our BBB platform technology licensed from F-star. Any future U.S. and foreign patents that may issue from this patent family (assuming the necessary non-provisional patent applications are timely filed and all other applicable requirements are satisfied) would be expected to expire in 2038, excluding any patent term adjustments and any patent term extensions.

ETV: IDS

We own two pending U.S. provisional applications directed to, among other things, our ETV:IDS constructs that incorporate our BBB platform technology licensed from F-star. Any future U.S. and foreign patents that may issue from this patent family (assuming the necessary non-provisional patent applications are timely filed and all other applicable requirements are satisfied) would be expected to expire in 2038, excluding any patent term adjustments and any patent term extensions.

LRRK2

We license multiple patent families from Genentech directed to, among other things, our LRRK2 program, including DNL201, DNL151 and other related compounds. These licensed patent families include approximately 10 granted U.S. patents, and approximately 155 granted foreign patents and 55 pending foreign patent applications. The issued patents in these licensed families are expected to expire in 2031, excluding any patent term adjustments and any patent term extensions.

DNL201

We license a patent family from Genentech directed to, among other things, DNL201, which includes one issued U.S. patent, and approximately 38 granted foreign patents and five pending foreign patent applications. The issued U.S. patent claims the composition of matter of DNL201 and is expected to expire in 2031, excluding any patent term adjustments and any patent term extensions.

DNL151

We own one patent family directed to DNL151, which includes one pending U.S. non-provisional patent application, one pending patent cooperation treaty, or PCT, application and two pending foreign patent applications, with pending claims covering the composition and use of DNL151. Future U.S. and foreign patents issued from this patent family are expected to expire in 2037, excluding any patent term adjustments and any patent term extensions. In addition, we license approximately 38 foreign patents from Genentech, with issued claims related to the DNL151 compound class. We do not own or in-license any issued U.S. patents covering the composition of matter of DNL151 specifically.

RIPK1

For our most advanced RIPK1 product candidate, DNL747, we own a patent family directed to the composition of matter of DNL747, which includes one issued U.S. patent, one pending U.S. non-provisional patent application, one PCT application and two pending foreign patent applications. Future U.S. and foreign patents issued from this patent family are expected to expire in 2037, excluding any patent term adjustments and any patent term extensions.

We cannot guarantee that our owned and licensed pending patent applications, or any patent applications that we may in the future file or license from third parties, will result in the issuance of patents. We also cannot predict the scope of claims that may be allowed or enforced in our patents. In addition, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Consequently, we may not obtain or maintain adequate patent protection for any of our programs and product candidates. For more information regarding the risks related to our intellectual property, see “Risk Factors—Risks Related to Our Intellectual Property.”

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a non-provisional patent application. In the United States, the patent term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. 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 applicable to an approved drug 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 provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our products receive FDA approval, we expect to apply for patent term extensions on patents covering those products. We plan to seek patent term extensions to any of our issued patents in any jurisdiction where these are available, however there is no guarantee that the applicable authorities, including the FDA in the United States, will agree with our assessment of whether such extensions should be granted, and if granted, the length of such extensions. For more information regarding the risks related to our intellectual property, see “Risk Factors—Risks Related to Our Intellectual Property.”

In addition to patent protection, we also rely on trademark registration, trade secrets, know how, other proprietary information and continuing technological innovation to develop and maintain our competitive position. We seek to protect and maintain the confidentiality of proprietary information to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection. Although we take steps to protect our proprietary information and trade secrets, including through contractual means with our employees and consultants, third parties may

independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or disclose our technology. Thus, we may not be able to meaningfully protect our trade secrets. It is our policy to require our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. These agreements provide that all confidential information concerning our business or financial affairs developed or made known to the individual during the course of the individual's relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. Our agreements with employees also provide that all inventions conceived by the employee in the course of employment with us or from the employee's use of our confidential information are our exclusive property. However, such confidentiality agreements and invention assignment agreements can be breached and we may not have adequate remedies for any such breach. For more information regarding the risks related to our intellectual property, see "Risk Factors—Risks Related to Our Intellectual Property."

The patent positions of biotechnology companies like ours are generally uncertain and involve complex legal, scientific and factual questions. Our commercial success will also depend in part on not infringing upon the proprietary rights of third parties. It is uncertain whether the issuance of any third-party patent would require us to alter our development or commercial strategies, or our drugs or processes, obtain licenses or cease certain activities. Our breach of any license agreements or our failure to obtain a license to proprietary rights required to develop or commercialize our future products may have a material adverse impact on us. If third parties prepare and file patent applications in the United States that also claim technology to which we have rights, we may have to participate in interference or derivation proceedings in the USPTO to determine priority of invention. For more information, see "Risk Factors—Risks Related to Our Intellectual Property."

Government Regulation

Government authorities in the United States at the federal, state and local level and in other countries regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, post-approval monitoring and reporting, marketing and export and import of drug and biological products. Generally, before a new drug or biologic can be marketed, considerable data demonstrating its quality, safety and efficacy must be obtained, organized into a format specific for each regulatory authority, submitted for review and approved by the regulatory authority.

U.S. Drug Development

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations, and biologics under the FDCA, the Public Health Service Act, or PHSA, and their implementing regulations. Both drugs and biologics also are subject to other federal, state and local statutes and regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or post-market may subject an applicant to administrative or judicial sanctions. These sanctions could include, among other actions, the FDA's refusal to approve pending applications, withdrawal of an approval, a clinical hold, untitled or warning letters, product recalls or market withdrawals, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement and civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

Any future product candidates must be approved by the FDA through either a new drug application, or NDA, or a biologics license application, or BLA, process before they may be legally marketed in the United States. The process generally involves the following:

- Completion of extensive preclinical studies in accordance with applicable regulations, including studies conducted in accordance with good laboratory practice, or GLP, requirements;
- Submission to the FDA of an IND, which must become effective before human clinical trials may begin;
- Approval by an independent institutional review board, or IRB, or ethics committee at each clinical trial site before each trial may be initiated;
- Performance of adequate and well-controlled human clinical trials in accordance with applicable IND regulations, good clinical practice, or GCP, requirements and other clinical trial-related regulations to establish the safety and efficacy of the investigational product for each proposed indication;
- Submission to the FDA of an NDA or BLA;
- A determination by the FDA within 60 days of its receipt of an NDA or BLA to accept the filing for review;
- Satisfactory completion of a FDA pre-approval inspection of the manufacturing facility or facilities where the drug or biologic will be produced to assess compliance with current good manufacturing practices, or cGMP, requirements to assure that the facilities, methods and controls are adequate to preserve the drug or biologic's identity, strength, quality and purity;
- Potential FDA audit of the preclinical and/or clinical trial sites that generated the data in support of the NDA or BLA;
- FDA review and approval of the NDA or BLA, including consideration of the views of any FDA advisory committee, prior to any commercial marketing or sale of the drug or biologic in the United States; and
- Compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy, or REMS, and the potential requirement to conduct post-approval studies.

The data required to support an NDA or BLA are generated in two distinct developmental stages: preclinical and clinical. The preclinical and clinical testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for any future product candidates will be granted on a timely basis, or at all.

Preclinical Studies and IND

The preclinical developmental stage generally involves laboratory evaluations of drug chemistry, formulation and stability, as well as studies to evaluate toxicity in animals, which support subsequent clinical testing. The sponsor must submit the results of the preclinical studies, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. An IND is a request for authorization from the FDA to administer an investigational product to humans, and must become effective before human clinical trials may begin.

Preclinical studies include laboratory evaluation of product chemistry and formulation, as well as *in vitro* and animal studies to assess the potential for adverse events and in some cases to establish a

rationale for therapeutic use. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations for safety/toxicology studies. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical studies, among other things, to the FDA as part of an IND. Some long-term preclinical testing, such as animal tests of reproductive adverse events and carcinogenicity, may continue after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time, the FDA raises concerns or questions related to one or more proposed clinical trials and places the trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

Clinical Trials

The clinical stage of development involves the administration of the investigational product to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the trial sponsor's control, in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria and the parameters to be used to monitor subject safety and assess efficacy. Each protocol, and any subsequent amendments to the protocol, must be submitted to the FDA as part of the IND. Furthermore, each clinical trial must be reviewed and approved by an IRB for each institution at which the clinical trial will be conducted to ensure that the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the informed consent form that must be provided to each clinical trial subject or his or her legal representative, and must monitor the clinical trial until completed. There also are requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries.

A sponsor who wishes to conduct a clinical trial outside of the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. If a foreign clinical trial is not conducted under an IND, the sponsor may submit data from the clinical trial to the FDA in support of an NDA or BLA. The FDA will accept a well-designed and well-conducted foreign clinical study not conducted under an IND if the study was conducted in accordance with GCP requirements and the FDA is able to validate the data through an onsite inspection if deemed necessary.

Clinical trials in the United States generally are conducted in three sequential phases, known as Phase 1, Phase 2 and Phase 3, and may overlap.

- Phase I clinical trials generally involve a small number of healthy volunteers or disease-affected patients who are initially exposed to a single dose and then multiple doses of the product candidate. The primary purpose of these clinical trials is to assess the metabolism, pharmacologic action, side effect tolerability and safety of the drug.
- Phase II clinical trials involve studies in disease-affected patients to determine the dose required to produce the desired benefits. At the same time, safety and further PK and PD information is collected, possible adverse effects and safety risks are identified and a preliminary evaluation of efficacy is conducted.
- Phase III clinical trials generally involve a large number of patients at multiple sites and are designed to provide the data necessary to demonstrate the effectiveness of the product for its intended use, its safety in use and to establish the overall benefit/risk relationship of the product and provide an adequate basis for product approval. These trials may include comparisons with placebo and/or other comparator treatments. The duration of treatment is often extended to mimic the actual use of a product during marketing.

Post-approval trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication. In certain instances, the FDA may mandate the performance of Phase 4 clinical trials as a condition of approval of an NDA or BLA.

Progress reports detailing the results of the clinical trials, among other information, must be submitted at least annually to the FDA and written IND safety reports must be submitted to the FDA and the investigators for serious and unexpected suspected adverse events, findings from other studies suggesting a significant risk to humans exposed to the drug, findings from animal or *in vitro* testing that suggest a significant risk for human subjects and any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure.

Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, if at all. The FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug or biologic has been associated with unexpected serious harm to patients. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether a trial may move forward at designated check points based on access to certain data from the trial. Concurrent with clinical trials, companies usually complete additional animal studies and also must develop additional information about the chemistry and physical characteristics of the drug or biologic as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product and, among other things, companies must develop methods for testing the identity, strength, quality and purity of the final product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that our product candidates do not undergo unacceptable deterioration over their shelf life.

NDA/BLA Review Process

Following completion of the clinical trials, data are analyzed to assess whether the investigational product is safe and effective for the proposed indicated use or uses. The results of preclinical studies and clinical trials are then submitted to the FDA as part of an NDA or BLA, along with proposed labeling, chemistry and manufacturing information to ensure product quality and other relevant data. In short, the NDA or BLA is a request for approval to market the drug or biologic for one or more specified indications and must contain proof of safety and efficacy for a drug or safety, purity and potency for a biologic. The application may include both negative and ambiguous results of preclinical studies and clinical trials, as well as positive findings. Data may come from company-sponsored clinical trials intended to test the safety and efficacy of a product's use or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and efficacy of the investigational product to the satisfaction of FDA. FDA approval of an NDA or BLA must be obtained before a drug or biologic may be marketed in the United States.

Under the Prescription Drug User Fee Act, or PDUFA, as amended, each NDA or BLA must be accompanied by a user fee. FDA adjusts the PDUFA user fees on an annual basis. According to the FDA's fee schedule, effective through September 30, 2016, the user fee for an application requiring clinical data, such as an NDA or BLA, is $2,380,100. PDUFA also imposes an annual product fee for human drugs and biologics (approximately $97,750) and an annual establishment fee (approximately $580,000) on facilities used to manufacture prescription drugs and biologics. Fee waivers or reductions

are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. Additionally, no user fees are assessed on NDAs or BLAs for products designated as orphan drugs, unless the product also includes a non-orphan indication.

The FDA reviews all submitted NDAs and BLAs before it accepts them for filing, and may request additional information rather than accepting the NDA or BLA for filing. The FDA must make a decision on accepting an NDA or BLA for filing within 60 days of receipt. Once the submission is accepted for filing, the FDA begins an in-depth review of the NDA or BLA. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has ten months, from the filing date, in which to complete its initial review of a new molecular-entity NDA or original BLA and respond to the applicant, and six months from the filing date of a new molecular-entity NDA or original BLA designated for priority review. The FDA does not always meet its PDUFA goal dates for standard and priority NDAs or BLAs, and the review process is often extended by FDA requests for additional information or clarification.

Before approving an NDA or BLA, the FDA will conduct a pre-approval inspection of the manufacturing facilities for the new product to determine whether they comply with cGMP requirements. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. The FDA also may audit data from clinical trials to ensure compliance with GCP requirements. Additionally, the FDA may refer applications for novel drug products or drug products which present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions, if any. The FDA is not bound by recommendations of an advisory committee, but it considers such recommendations when making decisions on approval. The FDA likely will reanalyze the clinical trial data, which could result in extensive discussions between the FDA and the applicant during the review process. After the FDA evaluates an NDA or BLA, it will issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete and the application will not be approved in its present form. A Complete Response Letter usually describes all of the specific deficiencies in the NDA or BLA identified by the FDA. The Complete Response Letter may require additional clinical data, additional pivotal Phase 3 clinical trial(s) and/or other significant and time-consuming requirements related to clinical trials, preclinical studies or manufacturing. If a Complete Response Letter is issued, the applicant may either resubmit the NDA or BLA, addressing all of the deficiencies identified in the letter, or withdraw the application. Even if such data and information are submitted, the FDA may decide that the NDA or BLA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data.

Orphan Drugs

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making the product available in the United States for this type of disease or condition will be recovered from sales of the product.

Orphan drug designation must be requested before submitting an NDA or BLA. After the FDA grants orphan drug designation, the identity of the therapeutic agent 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.

If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications to market the same drug for the same indication for seven years from the date of such approval, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity by means of greater effectiveness, greater safety or providing a major contribution to patient care or in instances of drug supply issues. Competitors, however, may receive approval of either a different product for the same indication or the same product for a different indication but that could be used off-label in the orphan indication. Orphan drug exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval before we do for the same product, as defined by the FDA, for the same indication we are seeking approval, or if a product candidate is determined to be contained within the scope of the competitor's product for the same indication or disease. If one of our products designated as an orphan drug receives marketing approval for an indication broader than that which is designated, it may not be entitled to orphan drug exclusivity. Orphan drug status in the European Union has similar, but not identical, requirements and benefits.

Expedited Development and Review Programs

The FDA has a fast track program that is intended to expedite or facilitate the process for reviewing new drugs and biologics that meet certain criteria. Specifically, new drugs and biologics are eligible for fast track designation if they are intended to treat a serious or life threatening condition and preclinical or clinical data demonstrate the potential to address unmet medical needs for the condition. Fast track designation applies to both the product and the specific indication for which it is being studied. The sponsor can request the FDA to designate the product for fast track status any time before receiving NDA or BLA approval, but ideally no later than the pre-NDA or pre-BLA meeting.

Any product submitted to the FDA for marketing, including under a fast track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. Any product is eligible for priority review if it treats a serious or life-threatening condition and, if approved, would provide a significant improvement in safety and effectiveness compared to available therapies.

A product may also be eligible for accelerated approval, if it treats a serious or life-threatening condition and generally provides a meaningful advantage over available therapies. In addition, it must demonstrate an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, or IMM, that is reasonably likely to predict an effect on IMM or other clinical benefit. As a condition of approval, the FDA may require that a sponsor of a drug or biologic receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. If the FDA concludes that a drug or biologic shown to be effective can be safely used only if distribution or use is restricted, it may require such post-marketing restrictions, as it deems necessary to assure safe use of the product.

Additionally, a drug or biologic may be eligible for designation as a breakthrough therapy if the product is intended, alone or in combination with one or more other drugs or biologics, to treat a serious or life-threatening condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over currently approved therapies on one or more clinically significant endpoints. The benefits of breakthrough therapy designation include the same benefits as fast track designation, plus intensive guidance from the FDA to ensure an efficient drug development program. Fast track designation, priority review, accelerated approval and breakthrough therapy designation do not change the standards for approval, but may expedite the development or approval process.

Abbreviated Licensure Pathway of Biological Products as Biosimilar or Interchangeable

The Patient Protection and Affordable Care Act, or PPACA, or Affordable Care Act, or ACA, signed into law in 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCIA, created an abbreviated approval pathway for biological products shown to be highly similar to an FDA-licensed reference biological product. The BPCIA attempts to minimize duplicative testing, and thereby lower development costs and increase patient access to affordable treatments. An application for licensure of a biosimilar product must include information demonstrating biosimilarity based upon the following, unless the FDA determines otherwise:

- analytical studies demonstrating that the proposed biosimilar product is highly similar to the approved product notwithstanding minor differences in clinically inactive components;
- animal studies (including the assessment of toxicity); and
- a clinical study or studies (including the assessment of immunogenicity and PK or PD) sufficient to demonstrate safety, purity and potency in one or more conditions for which the reference product is licensed and intended to be used.

In addition, an application must include information demonstrating that:

- the proposed biosimilar product and reference product utilize the same mechanism of action for the condition(s) of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism(s) of action are known for the reference product;
- the condition or conditions of use prescribed, recommended, or suggested in the labeling for the proposed biosimilar product have been previously approved for the reference product;
- the route of administration, the dosage form, and the strength of the proposed biosimilar product are the same as those for the reference product; and
- the facility in which the biological product is manufactured, processed, packed or held meets standards designed to assure that the biological product continues to be safe, pure, and potent.

Biosimilarity means that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and that there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product. In addition, the law provides for a designation of “interchangeability” between the reference and biosimilar products, whereby the biosimilar may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product. The higher standard of interchangeability must be demonstrated by information sufficient to show that:

- the proposed product is biosimilar to the reference product;
- the proposed product is expected to produce the same clinical result as the reference product in any given patient; and
- for a product that is administered more than once to an individual, the risk to the patient in terms of safety or diminished efficacy of alternating or switching between the biosimilar and the reference product is no greater than the risk of using the reference product without such alternation or switch.

FDA approval is required before a biosimilar may be marketed in the United States. However, complexities associated with the large and intricate structures of biological products and the process by which such products are manufactured pose significant hurdles to the FDA’s implementation of the law

that are still being worked out by the FDA. For example, the FDA has discretion over the kind and amount of scientific evidence—laboratory, preclinical and/or clinical—required to demonstrate biosimilarity to a licensed biological product.

The FDA intends to consider the totality of the evidence, provided by a sponsor to support a demonstration of biosimilarity, and recommends that sponsors use a stepwise approach in the development of their biosimilar products. Biosimilar product applications thus may not be required to duplicate the entirety of preclinical and clinical testing used to establish the underlying safety and effectiveness of the reference product. However, the FDA may refuse to approve a biosimilar application if there is insufficient information to show that the active ingredients are the same or to demonstrate that any impurities or differences in active ingredients do not affect the safety, purity or potency of the biosimilar product. In addition, as with BLAs, biosimilar product applications will not be approved unless the product is manufactured in facilities designed to assure and preserve the biological product's safety, purity and potency.

The submission of a biosimilar application does not guarantee that the FDA will accept the application for filing and review, as the FDA may refuse to accept applications that it finds are insufficiently complete. The FDA will treat a biosimilar application or supplement as incomplete if, among other reasons, any applicable user fees assessed under the Biosimilar User Fee Act of 2012 have not been paid. In addition, the FDA may accept an application for filing but deny approval on the basis that the sponsor has not demonstrated biosimilarity, in which case the sponsor may choose to conduct further analytical, preclinical or clinical studies and submit a BLA for licensure as a new biological product.

The timing of final FDA approval of a biosimilar for commercial distribution depends on a variety of factors, including whether the manufacturer of the branded product is entitled to one or more statutory exclusivity periods, during which time the FDA is prohibited from approving any products that are biosimilar to the branded product. The FDA cannot approve a biosimilar application for twelve years from the date of first licensure of the reference product. Additionally, a biosimilar product sponsor may not submit an application for four years from the date of first licensure of the reference product. A reference product may also be entitled to exclusivity under other statutory provisions. For example, a reference product designated for a rare disease or condition (an "orphan drug") may be entitled to seven years of exclusivity, in which case no product that is biosimilar to the reference product may be approved until either the end of the twelve-year period provided under the biosimilarity statute or the end of the seven-year orphan drug exclusivity period, whichever occurs later. In certain circumstances, a regulatory exclusivity period can extend beyond the life of a patent, and thus block biosimilarity applications from being approved on or after the patent expiration date. In addition, the FDA may under certain circumstances extend the exclusivity period for the reference product by an additional six months if the FDA requests, and the manufacturer undertakes, studies on the effect of its product in children, a so-called pediatric extension.

The first biological product determined to be interchangeable with a branded product for any condition of use is also entitled to a period of exclusivity, during which time the FDA may not determine that another product is interchangeable with the reference product for any condition of use. This exclusivity period extends until the earlier of: (1) one year after the first commercial marketing of the first interchangeable product; (2) 18 months after resolution of a patent infringement against the applicant that submitted the application for the first interchangeable product, based on a final court decision regarding all of the patents in the litigation or dismissal of the litigation with or without prejudice; (3) 42 months after approval of the first interchangeable product, if a patent infringement suit against the applicant that submitted the application for the first interchangeable product is still ongoing; or (4) 18 months after approval of the first interchangeable product if the applicant that submitted the application for the first interchangeable product has not been sued.

Post-Approval Requirements

Following approval of a new product, the manufacturer and the approved product are subject to continuing regulation by the FDA, including, among other things, monitoring and record-keeping requirements, requirements to report adverse experiences, and comply with promotion and advertising requirements, which include restrictions on promoting drugs for unapproved uses or patient populations (known as "off-label use") and limitations on industry-sponsored scientific and educational activities. Although physicians may prescribe legally available drugs for off-label uses, manufacturers may not market or promote such uses. Prescription drug promotional materials must be submitted to the FDA in conjunction with their first use. Further, if there are any modifications to the drug or biologic, including changes in indications, labeling or manufacturing processes or facilities, the applicant may be required to submit and obtain FDA approval of a new NDA/BLA or NDA/BLA supplement, which may require the development of additional data or preclinical studies and clinical trials.

The FDA may also place other conditions on approvals including the requirement for a Risk Evaluation and Mitigation Strategy, or REMS, to assure the safe use of the product. A REMS could include medication guides, physician communication plans or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. Any of these limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensing of products. Product approvals may be withdrawn for non-compliance with regulatory standards or if problems occur following initial marketing.

The FDA may withdraw approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical studies to assess new safety risks; or imposition of distribution restrictions or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical studies;
- refusal of the FDA to approve pending applications or supplements to approved applications;
- applications, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising, and promotion of products that are placed on the market. Drugs and biologics may be promoted only for the approved indications and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability.

Other U.S. Regulatory Matters

Manufacturing, sales, promotion and other activities following product approval are also subject to regulation by numerous regulatory authorities in the United States in addition to the FDA, including the Centers for Medicare & Medicaid Services, other divisions of the Department of Health and Human Services, the Department of Justice, the Drug Enforcement Administration, the Consumer Product Safety Commission, the Federal Trade Commission, the Occupational Safety & Health Administration, the Environmental Protection Agency and state and local governments.

For example, in the United States, sales, marketing and scientific and educational programs also must comply with state and federal fraud and abuse laws. These laws include the federal Anti-Kickback Statute, which makes it illegal for any person, including a prescription drug manufacturer (or a party acting on its behalf), to knowingly and willfully solicit, receive, offer or pay any remuneration that is intended to induce or reward referrals, including the purchase, recommendation, order or prescription of a particular drug, for which payment may be made under a federal healthcare program, such as Medicare or Medicaid. Violations of this law are punishable by up to five years in prison, criminal fines, administrative civil money penalties and exclusion from participation in federal healthcare programs. Moreover, the ACA provides that 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.

Pricing and rebate programs must comply with the Medicaid rebate requirements of the U.S. Omnibus Budget Reconciliation Act of 1990 and more recent requirements in the ACA. If products are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply. Products must meet applicable child-resistant packaging requirements under the U.S. Poison Prevention Packaging Act. Manufacturing, sales, promotion and other activities also are potentially subject to federal and state consumer protection and unfair competition laws.

The distribution of biologic and pharmaceutical products is subject to additional requirements and regulations, including extensive record-keeping, licensing, storage and security requirements intended to prevent the unauthorized sale of pharmaceutical products.

The failure to comply with any of these laws or regulatory requirements subjects firms to possible legal or regulatory action. Depending on the circumstances, failure to meet applicable regulatory requirements can result in criminal prosecution, fines or other penalties, injunctions, requests for recall, seizure of products, total or partial suspension of production, denial or withdrawal of product approvals or refusal to allow a firm to enter into supply contracts, including government contracts. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. Prohibitions or restrictions on sales or withdrawal of future products marketed by us could materially affect our business in an adverse way.

Changes in regulations, statutes or the interpretation of existing regulations could impact our business in the future by requiring, for example: (i) changes to our manufacturing arrangements; (ii) additions or modifications to product labeling; (iii) the recall or discontinuation of our products; or (iv) additional record-keeping requirements. If any such changes were to be imposed, they could adversely affect the operation of our business.

U.S. Patent-Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of FDA approval of any future product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act. The Hatch-Waxman Act permits restoration of the patent term of up to five years as compensation for patent term lost during product development and FDA regulatory review process. Patent-term restoration, however, cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent-term restoration period is generally one-half the time between the effective date of an IND and the submission date of an NDA or BLA plus the time between the submission date of an NDA or BLA and the approval of that application, except that the review period is reduced by any time during which the applicant failed to exercise due diligence. Only

one patent applicable to an approved drug is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The U.S. PTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may apply for restoration of patent term for our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant NDA or BLA.

Market exclusivity provisions under the FDCA also can delay the submission or the approval of certain applications. The FDCA provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant to gain approval of a NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application, or ANDA, or a 505(b)(2) NDA submitted by another company for another version of such drug where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement. The FDCA also provides three years of marketing exclusivity for a NDA, 505(b)(2) NDA or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example, new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the conditions of use associated with the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the original active agent. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

A reference biological product is granted twelve years of data exclusivity from the time of first licensure of the product, and the FDA will not accept an application for a biosimilar or interchangeable product based on the reference biological product until four years after the date of first licensure of the reference product. “First licensure” typically means the initial date the particular product at issue was licensed in the United States. Date of first licensure does not include the date of licensure of (and a new period of exclusivity is not available for) a biological product if the licensure is for a supplement for the biological product or for a subsequent application by the same sponsor or manufacturer of the biological product (or licensor, predecessor in interest, or other related entity) for a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device or strength, or for a modification to the structure of the biological product that does not result in a change in safety, purity, or potency. Therefore, one must determine whether a new product includes a modification to the structure of a previously licensed product that results in a change in safety, purity, or potency to assess whether the licensure of the new product is a first licensure that triggers its own period of exclusivity. Whether a subsequent application, if approved, warrants exclusivity as the “first licensure” of a biological product is determined on a case-by-case basis with data submitted by the sponsor.

European Union Drug Development

As in the United States, medicinal products can be marketed only if a marketing authorization from the competent regulatory agencies has been obtained.

Similar to the United States, the various phases of preclinical and clinical research in the European Union are subject to significant regulatory controls. Although the EU Clinical Trials Directive 2001/20/EC has sought to harmonize the EU clinical trials regulatory framework, setting out common

rules for the control and authorization of clinical trials in the EU, the EU Member States have transposed and applied the provisions of the Directive differently. This has led to significant variations in the member state regimes. Under the current regime, before a clinical trial can be initiated it must be approved in each of the EU countries where the trial is to be conducted by two distinct bodies: the National Competent Authority, or NCA, and one or more Ethics Committees, or ECs. Under the current regime all suspected unexpected serious adverse reactions to the investigated drug that occur during the clinical trial have to be reported to the NCA and ECs of the Member State where they occurred.

The EU clinical trials legislation currently is undergoing a transition process mainly aimed at harmonizing and streamlining clinical-trial authorization, simplifying adverse-event reporting procedures, improving the supervision of clinical trials and increasing their transparency. Recently enacted Clinical Trials Regulation EU No 536/2014 ensures that the rules for conducting clinical trials in the EU will be identical. In the meantime, Clinical Trials Directive 2001/20/EC continues to govern all clinical trials performed in the EU.

European Union Drug Review and Approval

In the European Economic Area, or EEA, which is comprised of the 27 Member States of the European Union (including Norway and excluding Croatia), Iceland and Liechtenstein, medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are two types of marketing authorizations.

- The Community MA is issued by the European Commission through the Centralized Procedure, based on the opinion of the Committee for Medicinal Products for Human Use, or CHMP, of the European Medicines Agency, or EMA, and is valid throughout the entire territory of the EEA. The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products, advanced-therapy medicines such as gene-therapy, somatic cell-therapy or tissue-engineered medicines and medicinal products containing a new active substance indicated for the treatment of HIV, AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and other immune dysfunctions and viral diseases. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU.
- National MAs, which are issued by the competent authorities of the Member States of the EEA and only cover their respective territory, are available for products not falling within the mandatory scope of the Centralized Procedure. Where a product has already been authorized for marketing in a Member State of the EEA, this National MA can be recognized in another Member States through the Mutual Recognition Procedure. If the product has not received a National MA in any Member State at the time of application, it can be approved simultaneously in various Member States through the Decentralized Procedure. Under the Decentralized Procedure an identical dossier is submitted to the competent authorities of each of the Member States in which the MA is sought, one of which is selected by the applicant as the Reference Member State, or RMS. The competent authority of the RMS prepares a draft assessment report, a draft summary of the product characteristics, or SPC, and a draft of the labeling and package leaflet, which are sent to the other Member States (referred to as the Member States Concerned) for their approval. If the Member States Concerned raise no objections, based on a potential serious risk to public health, to the assessment, SPC, labeling, or packaging proposed by the RMS, the product is subsequently granted a national MA in all the Member States (i.e., in the RMS and the Member States Concerned).

Under the above described procedures, before granting the MA, the EMA or the competent authorities of the Member States of the EEA make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

Coverage and Reimbursement

Sales of our products will depend, in part, on the extent to which our products will be covered by third-party payors, such as government health programs, commercial insurance and managed healthcare organizations. In the United States no uniform policy of coverage and reimbursement for drug or biological products exists. Accordingly, decisions regarding the extent of coverage and amount of reimbursement to be provided for any of our products will be made on a payor-by-payor basis. As a result, the coverage determination process is often a time-consuming and costly process that will 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 obtained.

The United States government, state legislatures and foreign governments have shown significant interest in implementing cost containment programs to limit the growth of government-paid health care costs, including price-controls, restrictions on reimbursement and requirements for substitution of generic products for branded prescription drugs. For example, the ACA contains provisions that may reduce the profitability of drug products through increased rebates for drugs reimbursed by Medicaid programs, extension of Medicaid rebates to Medicaid managed care plans, mandatory discounts for certain Medicare Part D beneficiaries and annual fees based on pharmaceutical companies' share of sales to federal health care programs. Adoption of general controls and measures, coupled with the tightening of restrictive policies in jurisdictions with existing controls and measures, could limit payments for pharmaceutical drugs.

The Medicaid Drug Rebate Program requires pharmaceutical manufacturers to enter into and have in effect a national rebate agreement with the Secretary of the Department of Health and Human Services as a condition for states to receive federal matching funds for the manufacturer's outpatient drugs furnished to Medicaid patients. The ACA made several changes to the Medicaid Drug Rebate Program, including increasing pharmaceutical manufacturers' rebate liability by raising the minimum basic Medicaid rebate on most branded prescription drugs from 15.1% of average manufacturer price, or AMP, to 23.1% of AMP and adding a new rebate calculation for "line extensions" (i.e., new formulations, such as extended release formulations) of solid oral dosage forms of branded products, as well as potentially impacting their rebate liability by modifying the statutory definition of AMP. The ACA also expanded the universe of Medicaid utilization subject to drug rebates by requiring pharmaceutical manufacturers to pay rebates on Medicaid managed care utilization and by enlarging the population potentially eligible for Medicaid drug benefits. The Centers for Medicare & Medicaid Services, or CMS, have proposed to expand Medicaid rebate liability to the territories of the United States as well.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, established the Medicare Part D program to provide a voluntary prescription drug benefit to Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities that provide coverage of outpatient prescription drugs. Unlike Medicare Part A and B, Part D coverage is not standardized. While all Medicare drug plans must give at least a standard level of coverage set by Medicare, Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of

the costs of prescription drugs may increase demand for products for which we receive marketing approval. However, any negotiated prices for our products covered by a Part D prescription drug plan likely will be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from the MMA may result in a similar reduction in payments from non-governmental payors.

For a drug product to receive federal reimbursement under the Medicaid or Medicare Part B programs or to be sold directly to U.S. government agencies, the manufacturer must extend discounts to entities eligible to participate in the 340B drug pricing program. The required 340B discount on a given product is calculated based on the AMP and Medicaid rebate amounts reported by the manufacturer. As of 2010, the ACA expanded the types of entities eligible to receive discounted 340B pricing, although, under the current state of the law, with the exception of children's hospitals, these newly eligible entities will not be eligible to receive discounted 340B pricing on orphan drugs. In addition, as 340B drug prices are determined based on AMP and Medicaid rebate data, the revisions to the Medicaid rebate formula and AMP definition described above could cause the required 340B discount to increase.

As noted above, the marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third-party payors fail to provide adequate coverage and reimbursement. An increasing emphasis on cost containment measures in the United States has increased and we expect will continue to increase the pressure on pharmaceutical pricing. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

In addition, in most foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing and reimbursement vary widely from country to country. For example, the European Union provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products. Historically, products launched in the European Union do not follow price structures of the United States and generally prices tend to be significantly lower.

Licenses and Collaborations

F-star License and Collaboration Agreement

Overview

In August 2016, we entered into a license and collaboration agreement with F-star Gamma Limited, f-star Biotechnologische Forschungs- und Entwicklungsges m.b.H and F-star Biotechnology Limited, or, collectively, F-star. The goal of the collaboration is the development of certain constant Fc domains of an antibody with non-native antigen binding activity, or Fcabs, to enhance delivery of therapeutics across the BBB into the brain. The collaboration leverages F-star's modular antibody technology and our expertise in the development of therapies for neurodegenerative diseases.

Under the terms of the F-star collaboration agreement, we can nominate up to three Fcab targets, or Accepted Fcab Targets, within the first three years of the date of the collaboration agreement; and

we have selected TfR as the first Accepted Fcab Target. With respect to each Accepted Fcab Target, we can nominate up to eight Fab targets, or Accepted Fab Targets, which are targets bound by the variable domains of an antibody or other therapeutic modalities, or Fabs. Under the F-star collaboration agreement, F-star is prohibited from developing, commercializing and manufacturing any antibody or other molecule that incorporates any Fcab directed to an Accepted Fcab Target, which we refer to as a Selected Fcab, or any Selected Fcab as a standalone product, and from authorizing any third party to take any such action until the expiration of our buy-out option, as described below. In addition, we are obligated to use commercially reasonable efforts during the research term to perform development activities in accordance with certain specified development plans.

Financial Obligations

We paid F-star Gamma an upfront fee of $5.5 million, which includes the selection of the first Accepted Fcab Target, TfR, under the collaboration. We are obligated to pay a one-time fixed fee in the low single-digit millions for each additional Accepted Fcab Target we select, technical milestone payments for each Accepted Fcab Target, up to a maximum of $15.0 million in the aggregate for all Accepted Fcab Targets, and, at specified times, monthly exclusivity fees for Accepted Fcab Targets and Accepted Fab Targets, which may be eliminated in certain circumstances. We are also responsible for certain research costs incurred by F-star 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.

Buy-Out Option

In connection with the entry into the F-star collaboration agreement, we also purchased an option for an upfront option fee of $0.5 million, which we refer to as the buy-out-option, to acquire all of the outstanding shares of F-star Gamma pursuant to a pre-negotiated buy-out option agreement. We must elect whether to exercise our buy-out option before the earlier of (i) dosing of the fifth patient dosed in the first Phase 1 trial of an antibody that binds to an Accepted Fab Target and an Accepted Fcab Target, (ii) the fourth anniversary of the first delivery by F-star of an Fcab meeting certain delivery criteria, and (iii) five and one half years after the delivery by us of a notice that we are progressing an Fcab identified from our library that binds to an Accepted Fcab Target. In addition, if we exercise the buy-out option, we will become an owner of certain intellectual property owned by F-star Gamma (by way of our ownership of F-star Gamma) and we will become a direct licensee of certain intellectual property of F-star Biotechnology (by way of our assumption of F-star Gamma's license agreement with F-star Biotechnology). If we exercise the buy-out option we will be obligated to make initial exercise payments under the buy-out option agreement and F-star Gamma's license agreement with F-star Biotechnology ranging from, in the aggregate, approximately $18.0 million to $50.0 million, plus a payment under the buy-out option agreement of the estimated net cash of F-star Gamma at the time of such exercise. In addition, we will be required under the buy-out option agreement and F-star Gamma's license agreement with F-star Biotechnology to make certain contingent payments upon the achievement of certain preclinical, clinical, regulatory and commercial milestones, up to a maximum amount of $447.0 million in the aggregate. The amount of the initial exercise and contingent payments varies based on whether F-star delivers an Fcab that meets pre-defined criteria, whether the Fcab has been identified solely by us or solely by F-star or jointly by us and F-star and the timing of our exercise of the buy-out option. Following exercise of the buy-out option, we will not be required to make any further milestone or royalty payments under the F-star collaboration agreement.

If we exercise the buy-out option, then f-star Biotechnologische Forschungs-und Entwicklungsges m.b.H and F-star Biotechnology will continue to be prohibited from developing, commercializing and manufacturing any antibody or other molecule that incorporates any Selected Fcab, or any Selected Fcab as a standalone product, and from authorizing any third party to take any such action.

If we do not exercise the buy-out option prior to the expiration of the buy-out option period, then, from the lapse of the buy-out option period until our rights with respect to an Accepted Fab Target expire or terminate, F-star is prohibited from developing, commercializing and manufacturing any antibody or other molecule that contains both a Selected Fcab and a Fab that specifically binds to the relevant Accepted Fab Target. In addition, in the event that we do not exercise the buy-out option prior to expiration of the buy-out option period, we have granted F-star Gamma a non-exclusive, royalty-free, irrevocable, perpetual, sublicensable license under our background and program intellectual property and any joint program intellectual property, to exploit any Fcab (other than one identified solely by us) against an Accepted Fcab Target and/or any antibody to the extent containing such Fcab (other than an Fcab identified solely by us or jointly with F-star), but excluding any rights to any Fabs and Accepted Fab Targets. If we elect not to exercise the buy-out option, we continue to have the option to obtain certain exclusive licenses as we describe further below.

License Option

With respect to each Accepted Fab Target, we have the right to obtain from F-star an exclusive, worldwide license to certain intellectual property to develop and commercialize licensed products that contain (i) a Fab that specifically binds to such Accepted Fab Target and (ii) an Fcab that we or F-star identify, either solely or jointly, and that specifically binds to an Accepted Fcab Target, for up to eight Accepted Fab Targets per each Accepted Fcab Target, as described above. Under each such license, we will be obligated to use commercially reasonable efforts to develop and commercialize the applicable licensed product in certain major market countries. If we do not exercise such a license option or otherwise elect to terminate it, such license option will generally expire upon the dosing of the fifth patient dosed in the first Phase 1 trial of the relevant antibody that binds to the applicable Accepted Fab Target.

Each time we exercise the license option described above, we will be obligated to pay F-star Gamma (i) a one-time fixed fee in the low single-digit millions, (ii) milestone payments upon the achievement of certain clinical development and commercial milestones, up to a maximum of $362.5 million in the aggregate; (iii) additional sales-based milestones if net sales of licensed products achieve certain specified levels, up to a maximum amount payable to F-star of $650.0 million in the aggregate and (iv) low-to-mid single-digit percentage royalties on net sales of licensed products. Our royalty payment obligations will expire on a country-by-country and licensed product-by-licensed product basis upon the later of (a) the expiration of the last valid claim of a licensed patent covering such licensed product in such country, (b) the expiration of regulatory exclusivity for such licensed product in such country, and (c) the twelfth anniversary of the first commercial sale of such licensed product in such country. Such amounts may be reduced by a specified percentage depending on the origin of the Fcab incorporated in the applicable licensed product and whether F-star delivers to us an Fcab that meets pre-defined criteria. We have the right to credit a certain amount of royalty payments that we pay to third parties with respect to certain licensed products against our royalty obligation to F-star Gamma but such credit cannot reduce our royalty obligation to F-star Gamma by more than fifty percent.

Other Rights

In addition to the buy-out option and option to obtain certain exclusive licenses described above, F-star Gamma and F-star Biotechnology granted us non-exclusive licenses under certain intellectual property to conduct technology development to discover and develop Fcabs. We also received a non-exclusive license under certain of F-star Biotechnology's platform patents and know-how to develop and commercialize products in connection with the delivery of therapeutics across the blood brain barrier, subject to certain specified restrictions.

F-star retains the right to use its intellectual property, including any intellectual property that we and F-star jointly own pursuant to the terms of the collaboration agreement, outside the scope of the

licenses granted to us. In addition, we granted F-star Biotechnology a non-exclusive, irrevocable, perpetual, sublicensable license under certain of our intellectual property to develop and commercialize certain of F-star's platform technology, subject to certain exclusivity obligations and the licenses granted to us under the collaboration agreement. Further, we are obligated to assign to F-star certain patents and know-how that we generate under the collaboration agreement related to F-star's platform technology or certain Fcabs identified solely by F-star.

Termination

Unless earlier terminated, the F-star collaboration agreement will remain in effect until all of our royalty and milestone payment obligations to F-star Gamma expire. Either party may terminate the F-star collaboration agreement if the other party materially breaches the collaboration agreement, subject to specified notice and cure provisions, or for the other party's bankruptcy or insolvency. In addition, F-star Gamma may terminate the F-star collaboration agreement if we challenge any of the patent rights licensed to us by F-star. We are able to terminate the F-star collaboration agreement for convenience, either in its entirety or on an Accepted Fcab Target-by-Accepted Fcab Target basis or an Accepted Fab Target-by-Accepted Fab Target basis, on 90 days' prior written notice to F-star.

Upon any termination by us for convenience or by F-star Gamma for our material uncured breach or insolvency, in each case either in whole or on an Accepted Fcab Target-by-Accepted Fcab Target or an Accepted Fab Target-by-Accepted Fab Target basis, among other things, the rights granted to us under the F-star collaboration agreement will terminate. Further, upon any such termination, if we have not exercised the buy-out option, (i) we must grant F-star Gamma certain non-exclusive, irrevocable and perpetual licenses under certain intellectual property owned by us arising out of the collaboration agreement to exploit certain antibodies that do not contain our proprietary Fabs or Fcabs identified solely by us, and (ii) F-star will no longer be restricted from developing and commercializing licensed products with respect to any terminated Accepted Fcab Target and/or Accepted Fab Target, as applicable.

Genentech Exclusive License Agreement

In June 2016, we entered into an exclusive license agreement with Genentech. The agreement gives us access to Genentech's preclinical stage LRRK2 small molecule program, which can be used to enhance and further progress our in-house LRRK2 program for Parkinson's disease. Under the agreement, Genentech granted us (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. We are obligated to use commercially reasonable efforts during the first three years of the agreement to research, develop and commercialize at least one licensed product.

Our financial obligations under the agreement with Genentech included an upfront payment of $8.5 million and a technology transfer fee of $1.5 million. In addition, we 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. In addition, we are obligated to pay 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 us, (ii) the date a compound was first discovered, derived or optimized by us, (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. We also have the right to credit a certain amount of third-party royalty and milestone payments against royalty and milestone payments owed to Genentech, but such credit cannot reduce our royalty obligation to Genentech by more than fifty percent. Our 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 or (b) the expiration of the last valid claim of a licensed patent covering such licensed product in such country. If one of our licensed products incorporates a compound provided to us by Genentech, has orphan drug exclusivity, and is not covered by a valid claim of a licensed patent, we must pay royalties on net sales of such licensed products on a country-by-country and licensed product-by-licensed product basis until such orphan drug exclusivity in such country expires, but our obligation to pay these royalties may be eliminated or reduced if there is a clinically superior product marketed in such country.

Unless earlier terminated, our agreement with Genentech will continue in effect until all of our royalty and milestone payment obligations to Genentech expire. Following expiration of the agreement, we will retain our licenses under the intellectual property Genentech licensed to us on a non-exclusive, royalty-free basis. Genentech may terminate the agreement if we challenge any of the patent rights licensed to us by Genentech, or if we materially breach the agreement, subject to specified notice and cure provisions, or enter into bankruptcy or insolvency proceedings. If Genentech terminates the agreement for our material breach, bankruptcy or insolvency after we have made a milestone payment to Genentech, then we are obligated to grant to Genentech an exclusive right of first negotiation with respect to certain of our patents, know-how and regulatory filings directed to Genentech-provided compounds. We do 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.

Scientific Advisory Board

We have assembled a highly qualified scientific advisory board comprised of advisors who have, collectively, deep expertise in neurodegenerative diseases, genomics, protein engineering, drug development and drug discovery as well as translational medicine. Our scientists work in collaboration with these advisors to identify new disease targets, develop a biomarker strategy, enhance our BBB platform technology and accelerate discovery and development.

Name	Affiliated Entity
Marc Tessier-Lavigne, Ph.D. (Chair)	Stanford University
Scott Biller, Ph.D.	Agios Pharmaceuticals
Alison Goate, DPhil	Mount Sinai
David Holtzman, M.D.	Washington University in St. Louis
Leonard Petrucelli, Ph.D.	Mayo Clinic
Eric Reiman, M.D.	Banner Alzheimer's Institute
Lee Rubin, Ph.D.	Harvard University
Kevan Shokat, Ph.D.	University of California San Francisco
Scott Small, M.D.	Columbia University
Huda Zoghbi, M.D.	Baylor University

Employees

As of September 30, 2017, we had approximately 125 employees, all of whom were full-time and around 100 of whom were engaged in research and development activities. Approximately two-thirds of our employees hold Ph.D. or M.D. degrees. Substantially all of our employees are located in South San Francisco, California. None of our employees are represented by a labor union or covered under a collective bargaining agreement.

Facilities

Our corporate headquarters are located in South San Francisco, California, where we lease approximately 38,000 square feet of office, research and development, engineering and laboratory space pursuant to a lease agreement which commenced on August 1, 2016 and expires on July 31, 2024, with an option to extend for 5 years. This facility houses all our personnel. We believe that our existing facilities are adequate for our near-term needs, but expect to need additional space as we grow. We believe that suitable additional or alternative space would be available as required in the future on commercially reasonable terms.

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.

MANAGEMENT

Executive Officers and Directors

The following table sets forth the names, ages and positions of our executive officers and directors as of November 24, 2017:

Name	Age	Position
Executive Officers:		
Ryan J. Watts, Ph.D.	41	President, Chief Executive Officer and Director
Alexander O. Schuth, M.D.	44	Chief Operating Officer and Secretary
Steve E. Krognes	49	Chief Financial Officer and Treasurer
Carole Ho, M.D.	44	Chief Medical Officer
Non-Employee Directors:		
Vicki Sato, Ph.D.(3)	69	Chairperson of our Board of Directors
Douglas Cole, M.D.(1)	57	Director
Jay Flatley(1)(2)	65	Director
Robert Nelsen(2)	54	Director
David Schenkein, M.D.(3)	60	Director
Marc Tessier-Lavigne, Ph.D.(2)	57	Director

(1) Member of the audit committee
(2) Member of the compensation committee
(3) Member of the corporate governance and nominating committee

Executive Officers

Ryan J. Watts, Ph.D. is one of our Co-Founders and has served as a member of our board of directors since March 2015 and as our President and Chief Executive Officer since August 2015. From March 2015 to August 2015, Dr. Watts acted as our interim President, Chief Scientific Officer and Head of Research and Development. Dr. Watts co-founded and joined Denali from Genentech, a biotechnology company, where he held various research and leadership roles of increasing responsibility between 2004 and 2015; from 2013 to February 2015, Dr. Watts served as Director of the Department of Neuroscience; from 2010 to 2013, Dr. Watts served as Associate Director of the Department of Neuroscience; and from 2004 to 2010, Dr. Watts led or served on numerous research and early development teams. In addition, Dr. Watts led Genentech's BBB team between 2009 and 2015, and he served as Chair of the Joint Research Committee with AC Immune between 2006 and 2010 (program currently in Phase 3) and between 2012 and 2014 (program currently in Phase 1). Dr. Watts received his Ph.D. in Biological Sciences from Stanford University and his B.S. in Biology from the University of Utah. Dr. Watts has authored and co-authored more than 60 scientific papers and has been an invited peer reviewer in numerous publications including *Cell, Nature Biotechnology, Nature Medicine, Neuron, Science* and *Science Translational Medicine*.

We believe Dr. Watts is qualified to serve on our board of directors because of the perspective and experience he provides as one of our founders and as our President and Chief Executive Officer, as well as his broad experience within the pharmaceutical industry, particularly in the area of neuroscience and drug discovery and development.

Alexander O. Schuth, M.D. is one of our Co-Founders and has served as our Chief Operating Officer since March 2015 and as Secretary since June 2015. Dr. Schuth co-founded and joined Denali from Genentech, where he held various roles of increasing responsibility between 2005 and 2015; from September 2014 to March 2015, Dr. Schuth served as Head of Technology Innovation and Diagnostics

Partnering; from March 2010 to September 2014, Dr. Schuth served as Head of Neuroscience Partnering; from January 2007 to March 2010, Dr. Schuth worked in the business development team; and from August 2005 to January 2007, Dr. Schuth worked as an R&D finance manager. From January 2001 to May 2003, he served as Investment Banking Associate in the equity capital markets group at Merrill Lynch in London. He currently serves on the board of directors of Molecular Health, a privately held biopharmaceutical company. Dr. Schuth received his M.B.A. from The Wharton School of the University of Pennsylvania and his M.D. from the Charite Medical School at the Humboldt University in Berlin, Germany.

Steve E. Krognes has served as our Chief Financial Officer since October 2015 and Treasurer since November 2015. Mr. Krognes joined Denali from Genentech, where he served as Chief Financial Officer and a member of the Executive Committee from April 2009 to September 2015. Mr. Krognes also oversaw Genentech's Site Services organization between 2011 and 2015, and Genentech's IT organization between 2009 and 2011. He chaired the Genentech Access to Care Foundation between 2009 and 2015. From January 2004 to April 2009, Mr. Krognes served as Head of Mergers & Acquisitions and a member of the Finance Executive Committee at Roche, a Swiss biotechnology company. From July 2002 to December 2003, Mr. Krognes served as Director of M&A at Danske Bank based in Norway. From April 2000 to June 2002, he served as a Venture Capitalist with Pylonia Ventures, a Swedish venture investments company. Prior to that, Mr. Krognes worked as a consultant at McKinsey and an investment banker at Goldman Sachs, based in London and Boston. Mr. Krognes currently serves as a member of the boards of directors of Corvus Pharmaceuticals, a biopharmaceutical company, RLS Global, a Swedish life science company, and the California Academy of Sciences, a private scientific and educational institution. Mr. Krognes served as a board member of the California Life Science Association between 2010 and 2015. He received his M.B.A. from Harvard Business School and his B.S. in Economics from The Wharton School of the University of Pennsylvania.

Carole Ho, M.D. has served as our Chief Medical Officer and Head of Development since June 2015. Dr. Ho joined Denali from Genentech, where she held various roles of increasing responsibility between 2007 and 2015; from October 2014 to June 2015, Dr. Ho served as Vice President, Non-Oncology Early Clinical Development; from November 2013 to October 2014, Dr. Ho served as Senior Group Medical Director, Early Clinical Development; from April 2011 to November 2013, Dr. Ho served as Group Medical Director, Early Clinical Development; from June 2009 to April 2011, Dr. Ho served as Group Medical Director Global Product Development (Inflammation); and from October 2007 to June 2009, Dr. Ho served as Medical Director, Early Clinical Development. From November 2006 to October 2007, Dr. Ho served as Associate Medical Director at Johnson & Johnson, a health care products company. From June 2002 to November 2006, she was an instructor in the Department of Neurology and Neurological Sciences at Stanford University. Dr. Ho completed a residency in neurology at Partners Neurology Residency of the Massachusetts General and Brigham and Women's Hospital and was board certified in neurology and psychiatry between 2004 and 2014. Dr. Ho received her M.D. from Cornell University and her B.S. in Biochemical Sciences from Harvard College.

Non-Employee Directors

Vicki Sato, *Ph.D.* has served as a member of our board of directors since April 2015 and as Chairperson of our board of directors since August 2016. From September 2006 until July 2017, Dr. Sato served as a professor of management practice at Harvard Business School. From July 2005 until October 2015, she also had an appointment as Professor of the Practice in the Department of Molecular and Cell Biology at Harvard University. From September 2000 to May 2005, Dr. Sato served as the President of Vertex Pharmaceuticals, a pharmaceutical company, with general management responsibility for business and corporate development, commercial operations, legal and finance, in addition to research and development. From 1992 until 2000, she served as the Chief Scientific Officer

and Senior Vice President of Research and Development of Vertex Pharmaceuticals. Dr. Sato joined Vertex Pharmaceuticals in 1992, after serving as Vice President of Research at Biogen, a biotechnology company, where she also served as a member of the Scientific Board. Dr. Sato serves on the boards of directors of Bristol Myers Squibb, Syros Pharmaceuticals and BorgWarner. She previously served on the board of directors of PerkinElmer until April 2017. Dr. Sato received her A.M. and Ph.D. degrees from Harvard University and her A.B. in Biology from Radcliffe College.

We believe Dr. Sato is qualified to serve on our board of directors because of her extensive industry experience and leadership experience as a senior executive and director of several life sciences companies.

Douglas Cole, *M.D.* has served as a member of our board of directors since May 2015. Dr. Cole joined Flagship Pioneering, which conceives, creates, resources and develops first-in-category life sciences companies, in 2001, and is currently Managing Partner, where he has focused on life science investments. He currently serves on the board of directors of Editas Medicine, a public biotechnology company, and serves on the board of directors of a number of private companies. Previously, Dr. Cole served on the boards of directors of Agios Pharmaceuticals, Receptos, AVEO Pharmaceuticals, Tetraphase Pharmaceuticals and Concert Pharmaceuticals. Dr. Cole received his M.D. from the University of Pennsylvania School of Medicine and his B.A. in English from Dartmouth College.

We believe Dr. Cole is qualified to serve on our board of directors because of his substantial experience as a venture capital investor in emerging life sciences companies, as well as his experience serving on the boards of directors for several life sciences companies.

Jay Flatley has served as a member of our board of directors since April 2015. Since July 2016, Mr. Flatley has served as the Executive Chairman of the board of directors of Illumina, a public company focused on sequencing- and array-based solutions for genetic analysis. From January 2016 to July 2016, he served as Illumina's Chairman and has served as a member of its board of directors since October 1999. From December 2013 to July 2016, Mr. Flatley served as the Chief Executive Officer of Illumina and as the President and Chief Executive Officer from October 1999 to December 2013. Prior to joining Illumina, Mr. Flatley was Co-founder, President, Chief Executive Officer, and a director of Molecular Dynamics, a life sciences company focused on genetic discovery and analysis, from July 1994 until its sale to Amersham Pharmacia Biotech in September 1998. Mr. Flatley is an advisory board member for U.C. San Diego's Moore Cancer Center and serves on the board of directors at Coherent, a photonics manufacturing company. Mr. Flatley received his B.S. and M.S. in Industrial Engineering from Stanford University and his B.A. in Economics from Claremont McKenna College.

We believe Mr. Flatley is qualified to serve on our board of directors because of his extensive leadership experience and industry knowledge.

Robert Nelsen has served as a member of our board of directors since May 2015. Mr. Nelsen has served as a Co-founder and Managing Director of ARCH Venture Partners, a venture capital firm focused on early-stage technology companies, or its affiliated entities, since 1986. Mr. Nelsen is a director of Juno Therapeutics, Sienna Biopharmaceuticals and Syros Pharmaceuticals, along with certain private companies. Previously, Mr. Nelsen served on the boards of directors of Agios Pharmaceuticals, KYTHERA Biopharmaceuticals, Adolor Corporation, Illumina, Fate Therapeutics, deCODE genetics, NeurogesX, Bellerophon Therapeutics, Sage Therapeutics and Caliper Life Sciences. He also previously served as trustee of Fred Hutchinson Cancer Research Center. Mr. Nelsen received his M.B.A. from the University of Chicago and his B.S. degrees in Economics and Biology from the University of Puget Sound.

We believe Mr. Nelsen is qualified to serve on our board of directors because of his experience as a venture capitalist building and serving on the boards of directors of many public and private emerging companies, including biotechnology companies.

David Schenkein, *M.D.* has served as a member of our board of directors since April 2015. Since August 2009, Dr. Schenkein has served as President and Chief Executive Officer of Agios Pharmaceuticals, a pharmaceuticals company. From April 2006 to July 2009, Dr. Schenkein served as a Senior Vice President of Oncology Development at Genentech. Dr. Schenkein currently serves on the boards of directors of Agios Pharmaceuticals and bluebird bio. Previously, Dr. Schenkein served on the board of directors of Foundation Medicine. He also currently serves as an adjunct attending physician in hematology at Tufts Medical Center. Dr. Schenkein received his M.D. from the State University of New York Upstate Medical School and his B.A. in Chemistry from Wesleyan University.

We believe that Dr. Schenkein is qualified to serve on our board of directors because of his extensive background in the biotechnology industry and leadership experience as a senior executive and director of biotechnology companies.

Marc Tessier-Lavigne, *Ph.D.* is one of our Co-Founders and has served as a member of our board of directors since March 2015. From March 2015 to August 2016, Dr. Tessier-Lavigne served as the Chairman of our board of directors. Since September 2016, Dr. Tessier-Lavigne has served as President of Stanford University. From March 2011 to September 2016, he served as President of the Rockefeller University, as well as professor and head of the Laboratory of Brain Development and Repair. From September 2003 to March 2011, Dr. Tessier-Lavigne served in positions of increasing responsibility at Genentech, where in 2009 he was named Executive Vice President for Research and Chief Scientific Officer. He currently serves on the board of directors of Regeneron Pharmaceuticals. Previously, he served on the boards of directors of Pfizer, Juno Therapeutics and Agios Pharmaceuticals. Dr. Tessier-Lavigne received his Ph.D. in Neurophysiology from University College London, his B.A. in Philosophy and Physiology from Oxford University and his B.Sc. in Physics from McGill University. He conducted postdoctoral work at the MRC Developmental Neurobiology Unit in London and at Columbia University.

We believe Dr. Tessier-Lavigne is qualified to serve on our board of directors because of his pioneering research, scientific knowledge, service on boards of directors of public companies in the life sciences industry and leadership in the biotechnology industry.

Board of Directors Composition

Our board of directors currently consists of seven members. After the completion of this offering, the number of directors will be fixed by our board of directors, subject to the terms of our amended and restated certificate of incorporation and amended and restated bylaws. Each of our current directors will continue to serve as a director until the election and qualification of his or her successor, or until his or her earlier death, resignation or removal.

Our amended and restated certificate of incorporation will provide that our board of directors will be divided into three classes with staggered three-year terms. Only one class of directors will be elected at each annual meeting of stockholders, with the other classes continuing for the remainder of their respective three-year terms. Our current directors will be divided among the three classes as follows:

- the Class I directors will be Drs. Cole and Tessier-Lavigne and Mr. Flatley, and their terms will expire at the annual meeting of stockholders to be held in 2018;
- the Class II directors will be Mr. Nelson and Dr. Sato, and their terms will expire at the annual meeting of stockholders to be held in 2019; and

- the Class III directors will be Drs. Schenkein and Watts, and their terms will expire at the annual meeting of stockholders to be held in 2020.

At each annual meeting of stockholders, upon the expiration of the term of a class of directors, the successor to each such director in the class will be elected to serve from the time of election and qualification until the third annual meeting following his or her election and until his or her successor is duly elected and qualified, in accordance with our amended and restated certificate of incorporation. Any additional directorships resulting from an increase in the number of directors will be distributed among the three classes so that, as nearly as possible, each class will consist of one-third of our directors.

This classification of our board of directors may have the effect of delaying or preventing changes in control of our company.

Director Independence

Upon the completion of this offering, our common stock will be listed on the NASDAQ Global Select Market, or NASDAQ. Under the rules of NASDAQ, independent directors must comprise a majority of a listed company's board of directors within one year of the completion of its initial public offering. In addition, the rules of NASDAQ require that, subject to specified exceptions, each member of a listed company's audit, compensation and corporate governance and nominating committees be independent. Audit committee members and compensation committee members must also satisfy the independence criteria set forth in Rule 10A-3 and Rule 10C-1, respectively, under the Exchange Act. Under the rules of NASDAQ, a director will only qualify as an "independent director" if, in the opinion of that company's board of directors, that person does not have a relationship that would interfere with the exercise of independent judgment in carrying out the responsibilities of a director.

To be considered to be independent for purposes of Rule 10A-3 and under the rules of NASDAQ, a member of an audit committee of a listed company may not, other than in his or her capacity as a member of the audit committee, the board of directors, or any other board of directors committee: (1) accept, directly or indirectly, any consulting, advisory, or other compensatory fee from the listed company or any of its subsidiaries; or (2) be an affiliated person of the listed company or any of its subsidiaries.

To be considered independent for purposes of Rule 10C-1 and under the rules of NASDAQ, the board of directors must affirmatively determine that the member of the compensation committee is independent, including a consideration of all factors specifically relevant to determining whether the director has a relationship to the company which is material to that director's ability to be independent from management in connection with the duties of a compensation committee member, including, but not limited to: (i) the source of compensation of such director, including any consulting, advisory or other compensatory fee paid by the company to such director; and (ii) whether such director is affiliated with the company, a subsidiary of the company or an affiliate of a subsidiary of the company.

Our board of directors undertook a review of its composition, the composition of its committees and the independence of our directors and considered whether any director has a material relationship with us that could compromise his or her ability to exercise independent judgment in carrying out his or her responsibilities. Based upon information requested from and provided by each director concerning his or her background, employment and affiliations, including family relationships, our board of directors has determined that Drs. Cole, Sato and Schenkein and Messrs. Flatley and Nelsen, representing five of our seven directors, do not have relationships that would interfere with the exercise of independent judgment in carrying out the responsibilities of a director and that each of these directors is "independent" as that term is defined under the rules of NASDAQ. Drs. Tessier-Lavigne

and Watts are not independent under NASDAQ's independence standards. We intend to rely on the phase-in rules of NASDAQ with respect to the independence of our compensation committee.

In making these determinations, our board of directors considered the current and prior relationships that each non-employee director has with our company and all other facts and circumstances our board of directors deemed relevant in determining their independence, including the beneficial ownership of our capital stock by each non-employee director, and the transactions involving them described in the section titled "Certain Relationships and Related Party Transactions." There are no family relationships among any of our directors or executive officers.

Board of Directors Leadership Structure

Our board of directors is currently chaired by Dr. Sato. As a general policy, our board of directors believes that separation of the positions of Chairperson and Chief Executive Officer reinforces the independence of our board of directors from management, creates an environment that encourages objective oversight of management's performance and enhances the effectiveness of our board of directors as a whole. As such, Dr. Watts serves as our President and Chief Executive Officer while Dr. Sato serves as the Chairperson of our board of directors but is not an officer. We expect and intend the positions of Chairperson of our board of directors and Chief Executive Officer to continue to be held by two separate individuals in the future.

Board of Directors Committees

Our board of directors has an audit committee, a compensation committee and a corporate governance and nominating committee, each of which has the composition and the responsibilities described below.

Audit Committee

The members of our audit committee are Dr. Cole and Mr. Flatley. Mr. Flatley is the chair of our audit committee, and is our audit committee financial expert, as that term is defined under the SEC rules implementing SOX Section 407, and possesses financial sophistication, as defined under the rules of NASDAQ. Following the completion of this offering, we will appoint a third independent director to serve on our audit committee in accordance with the rules of NASDAQ. Our audit committee oversees our corporate accounting and financial reporting process and assists our board of directors in monitoring our financial systems. Our audit committee will also:

- select and hire the independent registered public accounting firm to audit our financial statements;
- help to ensure the independence and performance of the independent registered public accounting firm;
- approve audit and non-audit services and fees;
- review financial statements and discuss with management and the independent registered public accounting firm our annual audited and quarterly financial statements, the results of the independent audit and the quarterly reviews and the reports and certifications regarding internal controls over financial reporting and disclosure controls;
- prepare the audit committee report that the SEC requires to be included in our annual proxy statement;
- review reports and communications from the independent registered public accounting firm;

- review the adequacy and effectiveness of our internal controls and disclosure controls and procedure;
- review our policies on risk assessment and risk management;
- review related party transactions; and
- establish and oversee procedures for the receipt, retention and treatment of accounting related complaints and the confidential submission by our employees of concerns regarding questionable accounting or auditing matters.

Our audit committee will operate under a written charter, to be effective prior to the completion of this offering, which will satisfy the applicable rules of the SEC and the listing standards of NASDAQ.

Compensation Committee

The members of our compensation committee are Mr. Flatley, Mr. Nelsen and Dr. Tessier-Lavigne. Dr. Tessier-Lavigne is the chair of our compensation committee. Dr. Tessier-Lavigne is not independent under NASDAQ's independence standards. We intend to rely upon the phase-in rules of NASDAQ with respect to the independence of our compensation committee. Our compensation committee oversees our compensation policies, plans and benefits programs. The compensation committee will also:

- oversee our overall compensation philosophy and compensation policies, plans and benefit programs;
- review and approve or recommend to our board of directors for approval compensation for our executive officers and directors;
- prepare the compensation committee report that the SEC will require to be included in our annual proxy statement; and
- administer our equity compensation plans.

Our compensation committee will operate under a written charter, to be effective prior to the completion of this offering, which will satisfy the applicable rules of the SEC and the listing standards of NASDAQ.

Corporate Governance and Nominating Committee

The members of our corporate governance and nominating committee are Dr. Sato and Dr. Schenkein. Dr. Sato is the chair of our corporate governance and nominating committee. Our corporate governance and nominating committee oversees and assists our board of directors in reviewing and recommending nominees for election as directors. Specifically, the corporate governance and nominating committee will:

- identify, evaluate and make recommendations to our board of directors regarding nominees for election to our board of directors and its committees;
- consider and make recommendations to our board of directors regarding the composition of our board of directors and its committees;
- review developments in corporate governance practices;
- evaluate the adequacy of our corporate governance practices and reporting; and
- evaluate the performance of our board of directors and of individual directors.

Our corporate governance and nominating committee will operate under a written charter, to be effective prior to the completion of this offering, which will satisfy the applicable rules of the SEC and the listing standards of NASDAQ.

Director Compensation

To date, none of our non-employee directors has received any cash compensation for serving on our board of directors, other than Mr. Flatley and Drs. Sato, Schenkein and Tessier-Lavigne, who each earn $30,000 annually, paid on a quarterly basis, for service as a member of our board of directors. From time to time, we have granted stock options or issued restricted stock to those non-employee directors who are also not affiliated with our venture fund investors for their service on our board of directors, and such grants were made in April 2015 to Mr. Flatley and Drs. Sato and Schenkein. An additional grant was made to Dr. Sato for her service as the Chairperson of our board of directors in August 2016. We also reimburse our directors for expenses associated with attending meetings of our board of directors and its committees.

The following table presents the total compensation each of our non-employee directors received during the year ended December 31, 2016. Other than as set forth in the table, we did not pay any compensation, make any equity awards or non-equity awards to or pay any other compensation to any of our non-employee directors in 2016.

	Fees Earned or Paid in Cash ($)	Option Awards ($) (1)	Total ($)
Vicki Sato, Ph.D.(2)	15,000	148,095	163,095
Douglas Cole, M.D.	—	—	—
Jay Flatley(3)	15,000	—	15,000
Stephen Knight, M.D.(4)	—	—	—
Robert Nelsen	—	—	—
David Schenkein, M.D.(5)	15,000	—	15,000
Marc Tessier-Lavigne, Ph.D.(6)	15,000	—	15,000
Stacie Weninger, Ph.D.(7)	—	—	—

(1) The amounts disclosed represent the aggregate grant date fair value of the award as calculated in accordance with FASB Accounting Standards Codification Topic 718, or ASC 718. The assumptions used in calculating the grant date fair value of the award disclosed in this column are set forth in the notes to our audited consolidated financial statements included elsewhere in this prospectus. These amounts do not correspond to the actual value that may be recognized by the directors upon vesting of the applicable awards.

(2) Dr. Sato is paid a quarterly cash retainer of $7,500 for her service on our board of directors. As of December 31, 2016, Dr. Sato held an option to purchase 37,500 shares of our common stock. One-third of the shares subject to the option vested on August 23, 2017, and two-thirds of the remaining shares vest annually thereafter, subject to continued service through each such vesting date. As of December 31, 2016, Dr. Sato held 75,000 restricted shares of our common stock. One-fourth of the shares subject to the restricted stock award vested on April 17, 2016, and one thirty-sixth of the remaining shares vest monthly thereafter, subject to continued service through each such vesting date.

(3) Mr. Flatley is paid a quarterly cash retainer of $7,500 for his service on our board of directors. As of December 31, 2016, Mr. Flatley held 75,000 restricted shares of our common stock. One-fourth of the shares subject to the restricted stock award vested on April 17, 2016, and one thirty-sixth of the remaining shares vest monthly thereafter, subject to continued service through each such vesting date.

(4) Dr. Knight resigned as a member of our board of directors on August 11, 2017.

(5) Dr. Schenkein is paid a quarterly cash retainer of $7,500 for his service on our board of directors. As of December 31, 2016, Dr. Schenkein held 75,000 restricted shares of our common stock. One-fourth of the shares subject to the restricted stock award vested on April 17, 2016, and one thirty-sixth of the remaining shares vest monthly thereafter, subject to continued service through each such vesting date.

(6) Dr. Tessier-Lavigne is paid a quarterly cash retainer of $7,500 for his service on our board of directors. As of December 31, 2016, Dr. Tessier-Lavigne held an aggregate of 3,114,043 restricted shares of our common stock. Of the total number of shares, 2,734,375 shares are subject to a restricted stock agreement whereby one-fourth of the shares vested on March 12, 2016, and one thirty-sixth of the remaining shares vest monthly thereafter, subject to continued service through each such vesting date. Of the total number of shares, 379,668 shares are subject to a restricted stock agreement whereby one-fourth of the shares vested on March 24, 2016, and one thirty-sixth of the remaining shares vest monthly thereafter, subject to continued service through each such vesting date.

(7) Dr. Weninger resigned as a member of our board of directors on August 11, 2017.

Directors who are also our employees receive no additional compensation for their service as directors. During 2016, Dr. Watts was our only employee director. See the section titled “Executive Compensation” for additional information about Dr. Watts’ compensation.

In November 2017, our board of directors adopted our outside director compensation policy. Members of our board of directors who are not employees are eligible for compensation under our outside director compensation policy. Our outside director compensation policy will be effective as of the effective date of the registration statement of which this prospectus forms a part. Under our outside director compensation policy, after the effective date of the registration statement of which this prospectus forms a part, each non-employee director will be eligible to receive compensation for his or her service consisting of annual cash retainers and equity awards as described below. Our board of directors may revise outside director compensation as it deems necessary or appropriate.

Cash Compensation

Under our outside director compensation policy, all non-employee directors will be entitled to receive the following cash compensation for their services following the effective date of the registration statement of which this prospectus forms a part:

- $40,000 per year for service as a board member;
- $30,000 per year additionally for service as non-executive chair of the board;
- $15,000 per year additionally for service as chair of the audit committee;
- $7,500 per year additionally for service as member of the audit committee (excluding committee chair);
- $10,000 per year additionally for service as chair of the compensation committee;
- $5,000 per year additionally for service as member of the compensation committee (excluding committee chair);
- $8,000 per year additionally for service as chair of the corporate governance and nominating committee;
- $4,000 per year additionally for service as member of the corporate governance and nominating committee (excluding committee chair);
- $10,000 per year additionally for service as chair of the science and technology committee; and

- $5,000 per year additionally for service as member of the science and technology committee (excluding committee chair).

All cash payments to non-employee directors who served in the relevant capacity at any point during the immediately preceding prior fiscal quarter will be paid quarterly in arrears on a prorated basis. A non-employee director who served in the relevant capacity during only a portion of the prior fiscal quarter will receive a pro-rated payment of the quarterly payment of the applicable cash retainer.

Equity Compensation

Beginning with the effective date of the registration statement of which this prospectus forms a part, nondiscretionary, automatic grants of stock options will be made to our non-employee directors under our outside director compensation policy. Under our 2017 Equity Incentive Plan, or 2017 Plan, no non-employee directors may be granted, in any fiscal year, awards with a grant date fair value (determined in accordance with U.S. generally accepted accounting principles) of more than $1 million, increased to $1.6 million in connection with his or her initial service. Any awards granted to an individual while he or she was an employee, or while he or she was a consultant but not a non-employee director, will not count for purposes of these limitations. Subject to these limitations:

- *Initial Award*. Each person who first becomes a non-employee director on or following the effective date of the registration statement of which this prospectus forms a part will be granted a nonstatutory stock option with a grant date value of $600,000 (with the shares covered by the award rounded down to the nearest whole share), or the Initial Award. The Initial Award will be granted on the date on which such person first becomes a non-employee director on or following the effective date of this offering. Subject to the terms of the policy, the Initial Award will vest and become exercisable as to 25% of the shares subject to the Initial Award on the one-year anniversary of the date of grant and as to 1/48th of the shares subject to the Initial Award on each monthly anniversary of the date of grant thereafter (and if there is no corresponding day, on the last day of the month), in each case, provided that the non-employee director continues to serve as a non-employee director through the applicable vesting date. A director who is an employee who ceases to be an employee director but who remains a director will not receive an Initial Award.
- *Continuing Director IPO Award*. Each person who serves as a non-employee director as of immediately prior to the effective date of the registration statement of which this prospectus forms a part and continues to serve as a non-employee director as of such effective date automatically will be granted a nonstatutory stock option with a grant date value of $600,000 (with the shares covered by the award rounded down to the nearest whole share), or the Continuing Director IPO Award. The Continuing Director IPO Award will be granted on the effective date of the registration statement of which this prospectus forms a part. Subject to the terms of the policy, the Continuing Director IPO Award will vest and become exercisable as to 25% of the shares subject to the Continuing Director IPO Award on the one-year anniversary of the date of grant and as to 1/48th of the shares subject to the Continuing Director IPO Award on each monthly anniversary of the date of grant thereafter (and if there is no corresponding day, on the last day of the month), in each case, provided that the non-employee director continues to serve as a non-employee director through the applicable vesting date.
- *Annual Award*. On the date of each annual meeting of stockholders beginning with the first annual meeting following the effective date of the registration statement of which this prospectus forms a part, each non-employee director who, as of such annual meeting date, has served on the board as a director for at least the preceding six months, automatically will be granted a nonstatutory stock option having a grant date value equal to $350,000 (with the shares covered by the award rounded down to the nearest whole share), or the Annual

Award. Any non-employee director who is not continuing as a director following the applicable annual meeting will not receive an Annual Award with respect to such annual meeting. Subject to the terms of the policy, the Annual Award will vest and become exercisable as to 100% of the shares subject to the Annual Award upon the earlier of the one year anniversary of the grant date or the day prior to our next annual meeting of stockholders occurring after the grant date, in each case, provided that the non-employee director continues to serve as a non-employee director through the applicable vesting date.

The grant date value of all the Initial Awards, Continuing Director IPO Awards and Annual Awards granted under our outside director compensation policy will be calculated in accordance with the Black-Scholes option valuation methodology or such other methodology as our board or the compensation committee of our board may determine prior to the grant of such award.

Non-employee directors are also eligible to receive all types of equity awards (except incentive stock options) under our 2017 Plan, including discretionary awards not covered under our outside director compensation policy.

Our 2017 Plan, as described below under the section titled “Executive Compensation-Employee Benefit and Stock Plans,” provides that in the event of a change in control, as defined in our 2017 Plan, where awards granted to non-employee directors are assumed or substituted for, if on the date of or following such assumption or substitution, the non-employee director’s status as a director or director of the successor corporation, as applicable, is terminated other than upon a voluntary resignation by the non-employee director (unless such resignation is at the request of the acquirer), then each outstanding equity award granted under our 2017 Plan to a non-employee director will fully vest, all restrictions on the shares subject to such award will lapse, and with respect to awards with performance-based vesting, all performance goals or other vesting criteria will be deemed achieved at 100% of target levels, and all of the shares subject to such award will become fully exercisable, if applicable, unless specifically provided otherwise under the applicable award agreement or other written agreement with the director.

Scientific Advisory Board Compensation

Each member of our scientific advisory board earns $10,000 annually for service as a member of our scientific advisory board. We also reimburse each member of our scientific advisory board for all reasonable and necessary expenses in connection with the performance of his or her services. In addition, we grant each new member an option to purchase 15,000 shares of our common stock, of which one-third of the shares vest on each anniversary of the date of commencement of service on the scientific advisory board. Members of the scientific advisory board who are also our employees or directors receive no additional compensation for their service on the scientific advisory board.

Compensation Committee Interlocks and Inside Participation

None of the members of our compensation committee is or has been an officer or employee of our company. None of our executive officers currently serves, or in the past fiscal year has served, as a member of the board of directors or compensation committee (or other board of directors committee performing equivalent functions or, in the absence of any such committee, the entire board of directors) of any entity that has one or more executive officers serving on our board of directors or compensation committee.

Code of Business Conduct and Ethics

We have adopted a written code of business conduct and ethics that applies to our directors, officers and employees, including our principal executive officer, principal financial officer, principal

accounting officer or controller, or persons performing similar functions. Following the completion of this offering, the code of business conduct and ethics will be available on our website at www.denalitherapeutics.com. We intend to disclose future amendments to such code, or any waivers of its requirements, applicable to any principal executive officer, principal financial officer, principal accounting officer or controller or persons performing similar functions or our directors on our website identified above. The inclusion of our website address in this prospectus does not include or incorporate by reference the information on our website into this prospectus.

Limitation of Liability and Indemnification

Our amended and restated certificate of incorporation and amended and restated bylaws, each to be effective upon the completion of this offering, will provide that we will indemnify our directors and officers, and may indemnify our employees and other agents, to the fullest extent permitted by Delaware law. Delaware law prohibits our amended and restated certificate of incorporation from limiting the liability of our directors for the following:

- any breach of the director's duty of loyalty to us or to our stockholders;
- acts or omissions not in good faith or that involve intentional misconduct or a knowing violation of law;
- unlawful payment of dividends or unlawful stock repurchases or redemptions; and
- any transaction from which the director derived an improper personal benefit.

If Delaware law is amended to authorize corporate action further eliminating or limiting the personal liability of a director, then the liability of our directors will be eliminated or limited to the fullest extent permitted by Delaware law, as so amended. Our amended and restated certificate of incorporation does not eliminate a director's duty of care and, in appropriate circumstances, equitable remedies, such as injunctive or other forms of non-monetary relief, remain available under Delaware law. This provision also does not affect a director's responsibilities under any other laws, such as the federal securities laws or other state or federal laws. Under our amended and restated bylaws, we will also be empowered to purchase insurance on behalf of any person whom we are required or permitted to indemnify.

In addition to the indemnification required in our amended and restated certificate of incorporation and amended and restated bylaws, we have entered into an indemnification agreement with each member of our board of directors and each of our officers. These agreements provide for the indemnification of our directors and officers for certain expenses and liabilities incurred in connection with any action, suit, proceeding or alternative dispute resolution mechanism, or hearing, inquiry or investigation that may lead to the foregoing, to which they are a party or other participant, or are threatened to be made a party or other participant, by reason of the fact that they are or were a director, officer, employee, agent or fiduciary of our company, by reason of any action or inaction by them while serving as an officer, director, agent or fiduciary, or by reason of the fact that they were serving at our request as a director, officer, employee, agent or fiduciary of another entity. In the case of an action or proceeding by or in the right of our company or any of our subsidiaries, no indemnification will be provided for any claim where a court determines that the indemnified party is prohibited from receiving indemnification. We believe that these charter and bylaw provisions and indemnification agreements are necessary to attract and retain qualified persons as directors and officers.

The limitation of liability and indemnification provisions in our amended and restated certificate of incorporation and amended and restated bylaws may discourage stockholders from bringing a lawsuit against directors for breach of their fiduciary duties. They may also reduce the likelihood of derivative

litigation against directors and officers, even though an action, if successful, might benefit us and our stockholders. Moreover, a stockholder's investment may be harmed to the extent we pay the costs of settlement and damage awards against directors and officers pursuant to these indemnification provisions. Insofar as indemnification for liabilities arising under the Securities Act may be permitted to our directors, officers and controlling persons pursuant to the foregoing provisions, or otherwise, we have been advised that, in the opinion of the SEC, such indemnification is against public policy as expressed in the Securities Act, and is, therefore, unenforceable. There is no pending litigation or proceeding naming any of our directors or officers as to which indemnification is being sought, nor are we aware of any pending or threatened litigation that may result in claims for indemnification by any director or officer.

EXECUTIVE COMPENSATION

Our named executive officers for 2016, which consist of our principal executive officer and the next three most highly compensated executive officers, are:

- Ryan J. Watts, Ph.D., our President and Chief Executive Officer;
- Alexander O. Schuth, M.D., our Chief Operating Officer and Secretary;
- Steve E. Krognes, our Chief Financial Officer and Treasurer; and
- Carole Ho, M.D., our Chief Medical Officer.

Summary Compensation Table

The following table sets forth information regarding the compensation of our named executive officers for the year ended December 31, 2016.

Name and Principal Position	Year	Salary ($)	Bonus ($)	Option Awards ($)(1)	Total ($)
Ryan J. Watts, Ph.D. *President and Chief Executive Officer*	2016	$450,000	$157,500(2)	$ —	$ 607,500
Alexander O. Schuth, M.D. *Chief Operating Officer and Secretary*	2016	$350,000	$122,500(2)	$ —	$ 472,500
Steve E. Krognes *Chief Financial Officer and Treasurer*	2016	$425,000	$398,750(3)	$ —	$ 823,750
Carole Ho, M.D. *Chief Medical Officer*	2016	$395,000	$138,250(2)	$495,600	$1,028,850

(1) The amounts disclosed represent the aggregate grant date fair value of the award as calculated in accordance with ASC 718. The assumptions used in calculating the grant date fair value of the award disclosed in this column are set forth in the notes to our audited consolidated financial statements included elsewhere in this prospectus. These amounts do not correspond to the actual value that may be recognized by the named executive officers upon vesting of the applicable awards.

(2) The amount reported represents a bonus based upon the achievement of company objectives for the year ended December 31, 2016, which was paid in January 2017.

(3) The amount reported represents (i) the portion of the sign-on bonus from 2015 of $250,000, which was earned in October 2016 pursuant to the terms of Mr. Krognes' employment agreement and (ii) a bonus of $148,750 based upon the achievement of company objectives for the year ended December 31, 2016, which was paid in January 2017. Had Mr. Krognes' employment been terminated by us for cause or by Mr. Krognes other than for good reason, in each case before October 1, 2016, he would have been required to repay the signing bonuses paid to him, including the $250,000 that was paid to him upon the commencement of his employment with us on October 1, 2015.

Outstanding Equity Awards at Fiscal Year-End

The following table sets forth information concerning outstanding equity awards held by each of our named executive officers as of December 31, 2016:

		Option Awards					Stock Awards	
Name	Grant Date [1]	Number of Securities Underlying Unexercised Options (#) Exercisable	Number of Securities Underlying Unexercised Options (#) Unexercisable	Equity incentive awards: number of securities underlying unexercised unearned options (#)	Option Exercise Price ($) [2]	Option Expiration Date	Number of Shares of Stock That Have Not Vested (#)	Market Value of Shares of Stock That Have Not Vested ($) [3]
Ryan J. Watts, Ph.D.	03/13/2015	—	—	—	—	—	1,333,008[4]	7,038,282
	08/21/2015	—	—	1,245,617[5]	0.68	8/20/2025	—	—
	08/21/2015	—	—	—	—	—	185,088[4]	977,265
Alexander O. Schuth, M.D.	03/13/2015	—	—	—	—	—	457,996[6]	2,418,219
	08/21/2015	—	—	249,123[5]	0.68	8/20/2025	—	—
	08/21/2015	—	—	—	—	—	63,596[6]	335,787
Steve E. Krognes	11/20/2015	—	—	125,000[5]	0.68	11/19/2025	—	—
	11/20/2015	—	—	—	—	—	354,166[7]	1,869,996
Carole Ho, M.D.	08/21/2015	—	—	125,000[5]	0.68	8/20/2025	—	—
	08/21/2015	—	—	—	—	—	156,250[8]	825,000
	07/02/2016	—	125,000[9]	—	5.28	7/01/2026	—	—

(1) Each of the outstanding options to purchase shares of our common stock was granted pursuant to our 2015 Plan.

(2) This column represents the fair market value of a share of our common stock on the date of grant, as determined by our board of directors or its authorized committee.

(3) Because our common stock was not traded on a public market on December 31, 2016, the market value has been calculated based on an estimated per-share common stock value of $5.28 per share as of December 31, 2016.

(4) One-fourth of the total number of shares subject to each restricted stock grant vested on February 23, 2016, and one thirty-sixth of the remaining shares subject to each restricted stock grant is scheduled to vest monthly thereafter, subject to continued service to us through each such vesting date. In the event of a change of control, the vesting of the shares subject to the restricted stock grants shall be accelerated in part so that the number of shares, if any, that would otherwise have first become vested in the period between the date of change of control and the date on which all but the unvested shares that would have vested in the final 12 months of the vesting period shall have first become vested shall immediately become vested. The remaining number of shares representing the last 12 months of vesting shall continue to vest in accordance with the original vesting schedule within the next 12 months set forth in the award agreement, provided, however, that each such award shall be immediately vested in full if on or within 12 months following the consummation of the change of control, Dr. Watts' employment with us is terminated without cause by us or by Dr. Watts for good reason, subject to Dr. Watts' execution of a release of claims in our favor and the terms and conditions of the Severance Plan, as described below.

(5) The shares subject to the option will vest upon certain performance goals being met as follows, in each case subject to the named executive officer's continued service to us: (a) 50% of the shares subject to the option vest upon (i) the date on which the reported closing price of our common stock on NASDAQ or the New York Stock Exchange (or other national securities exchange) has, for 90 consecutive trading days, equaled or exceeded $40.00 per share (subject to adjustments for any stock split, reverse stock split or certain other changes in capitalization), with the first day of the 90-day measurement period no earlier than the date that is 180 days after our initial public offering for our common stock, or (ii) the date on which we close a change of control (as defined in the applicable award agreement) transaction in which the stockholders receive consideration equal to no less than $40.00 per share (subject to adjustments for any stock split, reverse stock split or certain other changes in capitalization) in exchange for the sale of their capital stock and (b) 50% of the shares subject to the option vest upon (i) the date on which the reported closing price of our common

stock on NASDAQ or the New York Stock Exchange (or other national securities exchange) has, for 90 consecutive trading days, equaled or exceeded $80.00 per share (subject to adjustments for any stock split, reverse stock split or certain other changes in capitalization), with the first day of the 90-day measurement period no earlier than the date that is 180 days after our initial public offering for our common stock, or (ii) the date on which we close a change of control transaction in which the stockholders receive consideration equal to no less than $80.00 per share (subject to adjustments for any stock split, reverse stock split or certain other changes in capitalization) in exchange for the sale of their capital stock.

(6) The shares subject to each restricted stock grant will vest as follows, in each case subject to Dr. Schuth's continued service to us: (a) 54.54% of the total number of shares subject to each restricted stock grant, or Tranche 1, vested as to one-fourth of the original number of Tranche 1 shares on March 17, 2016, and then as to 1/36 of the remaining number of shares of Tranche 1 each month thereafter and (b) 45.46% of the total number of shares subject to each restricted stock grant, or Tranche 2, shall vest on March 17, 2018. In the event of a change of control, the vesting of the shares subject to each restricted stock grant shall be accelerated in part so that the number of shares, if any, that would otherwise have first become vested in the period between the date of change of control and the date on which all but the unvested shares that would have vested in the final 12 months of the vesting period shall have first become vested shall immediately become vested. The remaining number of shares representing the last 12 months of vesting shall continue to vest in accordance with the original vesting schedule within the next 12 months set forth in the award agreement, provided, however, that each such award shall be immediately vested in full if on or within 12 months following the consummation of the change of control, Dr. Schuth's employment with us is terminated without cause by us or by Dr. Schuth for good reason, subject to Dr. Schuth's execution of a release of claims in our favor and the terms and conditions of the Severance Plan, as described below.

(7) The shares were acquired pursuant to an early exercise provision and remain subject to our repurchase right in accordance with the vesting schedule of the options. One-fourth of the total number of shares subject to the option vested on October 1, 2016, and one thirty-sixth of the remaining shares vest monthly thereafter, subject to continued service to us through each such vesting date. In the event of a change of control, the vesting of these shares shall be accelerated in part so that the number of shares, if any, that would otherwise have first become vested in the period between the date of change of control and the date on which all but the unvested shares that would have vested in the final 12 months of the vesting period shall have first become vested shall immediately become vested. The remaining number of shares representing the last 12 months of vesting shall continue to vest in accordance with the original vesting schedule within the next 12 months set forth in the equity award agreement, provided however that the shares shall be immediately vested in full if on or within 12 months following the consummation of the change of control, Mr. Krognes' employment with us is terminated without cause by us or by Mr. Krognes for good reason, subject to Mr. Krognes' execution of a release of claims in our favor and the terms and conditions of the Severance Plan, as described below.

(8) The shares were acquired pursuant to an early exercise provision and remain subject to our repurchase right in accordance with the vesting schedule of the options. One-fourth of the total number of shares subject to the option vested on June 19, 2016, and one thirty-sixth of the remaining shares vest monthly thereafter, subject to continued service to us through each such vesting date. In the event of a change of control, the vesting of these shares shall be accelerated in part so that the number of shares, if any, that would otherwise have first become vested in the period between the date of change of control and the date on which all but the unvested shares that would have vested in the final 12 months of the vesting period shall have first become vested shall immediately become vested and exercisable. The remaining number of shares representing the last 12 months of vesting shall continue to vest in accordance with the original vesting schedule within the next 12 months set forth in the equity award agreement, provided however that the shares shall be immediately vested in full if on or within 12 months following the consummation of the change of control, Dr. Ho's employment with us is terminated without cause by us or by Dr. Ho for good reason, subject to Dr. Ho's execution of a release of claims in our favor and the terms and conditions of the Severance Plan, as described below.

(9) One-fourth of the total number of shares subject to the option vested on July 2, 2017, and one thirty-sixth of the remaining shares vest monthly thereafter, subject to continued service to us through each such vesting date. In the event of a change of control, the vesting of these shares shall be accelerated in part so that the number of shares, if any, that would otherwise have first become vested in the period between the date of change of control and the date on which all but the unvested shares that would have vested in the final 12 months of the vesting period shall have first become vested shall immediately become vested and exercisable. The remaining number of shares representing the last 12 months of vesting shall continue to vest

in accordance with the original vesting schedule within the next 12 months set forth in the equity award agreement, provided however that the shares shall be immediately vested in full if on or within 12 months following the consummation of the change of control, Dr. Ho's employment with us is terminated without cause by us or by Dr. Ho for good reason, subject to Dr. Ho's execution of a release of claims in our favor and the terms and conditions of the Severance Plan, as described below.

Non-Equity Incentive Plan Compensation

Each of our named executive officers was awarded a discretionary annual cash bonus for 2016 based on attainment of corporate objectives for 2016. The 2016 target bonus amounts for each named executive officer (35% of base salary for each named executive officer), along with a target bonus pool equal to 100% of all employees' target bonuses, and the related 2016 corporate objectives, were recommended by the compensation committee of our board of directors to our board of directors in mid-2015 and approved by our board of directors in November 2015. The corporate objectives were comprised of key short-term and long-term goals of one or more facets of our business relating to research and development, hiring goals, finance, corporate development and operations. At the same time, our board of directors determined that if at least 70% of the corporate objectives were achieved by the end of the 2016 calendar year, the bonus pool would be funded at 100%.

In November 2016, the compensation committee of our board of directors reviewed the progress against the applicable 2016 corporate objectives, determined that 73% of the performance objectives had been met to such date and recommended that our board of directors fully fund the cash bonus pool at 100% of target levels. After taking into consideration these recommendations and our board of directors' own review, our board of directors approved the full 2016 bonus pool funding, and the payment of 100% of target bonuses to our named executive officers from such pool, subject to each such officer's continued employment through the bonus payment date. Each of our named executive officers received 100% of his or her target bonus amount in January 2017. Following the end of 2016, management assessed the full year achievement against the 2016 corporate goals, and determined that 76% of such goals had ultimately been achieved. The amounts in the Summary Compensation Table under the column "Non-Equity Incentive Plan Compensation" are based on the bonuses awarded under the above-described 2016 bonus program.

Employment Arrangements with Our Named Executive Officers

Ryan J. Watts, Ph.D.

On November 10, 2017, we entered into a confirmatory employment letter with Dr. Watts, our President and Chief Executive Officer. The confirmatory employment letter has no specific term and provides for at-will employment. Dr. Watts' current annual base salary is $504,250 and Dr. Watts is considered annually for a target bonus of 55% of his annual base salary, subject to the terms and conditions of a bonus plan approved by our board of directors. The confirmatory offer letter also provides that we may, in our discretion, grant additional bonus amounts to Dr. Watts.

Alexander O. Schuth, M.D.

On November 10, 2017, we entered into a confirmatory employment letter with Dr. Schuth, our Chief Operating Officer and Secretary. The confirmatory employment letter has no specific term and provides for at-will employment. Dr. Schuth's current annual base salary is $380,250 and Dr. Schuth is considered annually for a target bonus of 40% of his annual base salary, subject to the terms of the applicable bonus plan developed by our chief executive officer and approved by our board of directors. The confirmatory offer letter also provides that we may, in our discretion, grant additional bonus amounts to Dr. Schuth.

Steve E. Krognes

On November 10, 2017, we entered into a confirmatory employment letter with Mr. Krognes, our Chief Financial Officer and Treasurer. The confirmatory employment letter has no specific term and provides for at-will employment. Mr. Krognes' current annual base salary is $437,750 and Mr. Krognes is considered annually for a target bonus of 40% of his annual base salary, subject to the terms of the applicable bonus plan developed by our chief executive officer and approved by our board of directors.

In addition, Mr. Krognes was previously awarded a one-time signing bonus of $500,000. Had Mr. Krognes' employment been terminated by us for cause or by Mr. Krognes other than for good reason, in each case before October 1, 2016, he would have been required to repay the signing bonus paid to him. The confirmatory offer letter also provides that we may, in our discretion, grant additional bonus amounts to Dr. Krognes.

Carole Ho, M.D.

On November 10, 2017, we entered into a confirmatory employment letter with Dr. Ho, our Chief Medical Officer. The confirmatory employment letter has no specific term and provides for at-will employment. Dr. Ho's current annual base salary is $406,850 and Dr. Ho is considered annually for a target bonus of 40% of her annual base salary, subject to the terms of the applicable bonus plan developed by our chief executive officer and approved by our board of directors.

In addition, Dr. Ho was previously awarded a one-time signing bonus of $199,033. Had Dr. Ho's employment been terminated by us for cause or by Dr. Ho other than for good reason, in each case before June 25, 2016, she would have been required to repay the signing bonus paid to her. The confirmatory offer letter also provides that we may, in our discretion, grant additional bonus amounts to Dr. Ho.

Potential Payments upon Termination or Change of Control

Our board of directors approved the following change of control and severance benefits for our executive officers (Dr. Watts, Dr. Schuth, Mr. Krognes and Dr. Ho) and other key employees pursuant to our Key Executive Change in Control and Severance Plan, or the Severance Plan.

If we terminate an executive officer's employment other than for "cause," death or "disability" or such participant resigns for "good reason" during the period beginning on a "change in control" (as such terms are defined in the Severance Plan) and ending 12 months following a change in control (the "change in control period"), such executive officer will be eligible to receive the following severance benefits (less applicable tax withholdings):

- 100% (150% for Dr. Watts) of the executive officer's annual base salary as in effect immediately prior to the termination (or if the termination is due to a resignation for good reason based on a material reduction in base salary, then the executive officer's annual base salary in effect immediately prior to such reduction) paid over 12 months (18 months for Dr. Watts);
- A lump sum payment equal to 100% of the annual target bonus the executive officer would otherwise be eligible to receive for the fiscal year in which the termination occurs, assuming achievement of all target levels at 100%;
- A lump sum cash payment in an aggregate amount equal to 12 months (18 months for Dr. Watts) of the applicable monthly premium cost that the executive officer otherwise would be required to pay to continue qualifying health coverage under COBRA (provided that if the Company determines in its sole discretion that these payments cannot be provided without violating applicable law, these payments will not be made); and

- 100% of the executive officer's then-outstanding and unvested equity awards that are subject to vest solely on the executive officer's continued service through the scheduled vesting dates will become vested in full and, if applicable, exercisable.

If we terminate an executive officer's employment other than for cause, death or disability or such participant resigns for good reason outside of the change in control period, such executive officer will be eligible to receive the following severance benefits (less applicable tax withholdings):

- 75% (100% for Dr. Watts) of the executive officer's annual base salary as in effect immediately prior to the termination (or if the termination is due to a resignation for good reason based on a material reduction in base salary, then the executive officer's annual base salary in effect immediately prior to such reduction) paid over nine months (12 months for Dr. Watts);
- A lump sum payment equal to the annual target bonus the executive officer would otherwise be eligible to receive for the fiscal year in which the termination occurs, assuming achievement of all annual targets at 100%, prorated for the portion of the year during which the executive officer was employed; and
- A lump sum cash payment in an aggregate amount equal to nine months (12 months for Dr. Watts) of the applicable monthly premium cost that the executive officer otherwise would be required to pay to continue qualifying health coverage under COBRA (provided that if the Company determines in its sole discretion that these payments cannot be provided without violating applicable law, these payments will not be made).

To receive the severance benefits upon a qualifying termination, an executive officer must sign and not revoke a form of separation agreement and release of claims in a form reasonably satisfactory to us within the timeframe set forth in the Severance Plan and must continue to comply with the provisions of such release and the terms of any confidentiality, proprietary information and inventions agreement and any other written agreement or agreements between the executive officer and us under which the executive officer has a material duty or obligation to us.

In addition, in the event of a change in control, the vesting schedule of any then-outstanding and unvested equity awards that are subject to time-based vesting and were granted to an executive officer prior to the effective date of the Severance Plan, will be accelerated in part so that the number of shares, if any, subject to each such award that would otherwise have first become vested in the period between the date of the consummation of the change in control and the date on which all but the final 12 months of the vesting period will have first become vested will immediately become vested and exercisable, as applicable. The remaining shares subject to each such award will continue to be eligible to vest in accordance with the original vesting schedule within the next 12 months as set forth in the applicable award agreement, and may accelerate in connection with certain terminations of employment, as described above.

If any of the payments provided for under the Severance Plan or otherwise payable to an executive officer would constitute "parachute payments" within the meaning of Section 280G of the Code and would be subject to the related excise tax under Section 4999 of the Code, then the executive officer will be entitled to receive either full payment of benefits or such lesser amount which would result in no portion of the benefits being subject to the excise tax, whichever results in the greater amount of after-tax benefits to him or her. The Severance Plan does not require us to provide any tax gross-up payments to any executive officer.

Employee Benefit and Stock Plans

2017 Equity Incentive Plan

Our board of directors adopted, and our stockholders approved, our 2017 Plan. Our 2017 Plan became effective on the business day immediately prior to the effective date of the registration statement of which this prospectus forms a part. Our 2017 Plan provides for the grant of incentive stock options, within the meaning of Section 422 of the Code, to our employees and any parent and subsidiary corporations' employees, and for the grant of nonstatutory stock options, restricted stock, restricted stock units, stock appreciation rights, performance units and performance shares to our employees, directors and consultants and our parent and subsidiary corporations' employees and consultants.

Authorized Shares. A total of 6,210,000 shares of our common stock has been reserved for issuance pursuant to our 2017 Plan. In addition, the shares reserved for issuance under our 2017 Plan also will include (a) those shares reserved but unissued under our 2015 Plan as of immediately prior to the termination of the 2015 Plan, and (b) shares subject to awards under our 2015 Plan that, on or after the termination of the 2015 Plan, expire or terminate and shares previously issued pursuant to our 2015 Plan, as applicable, that, on or after the termination of the 2015 Plan, are forfeited or repurchased by us (provided that the maximum number of shares that may be added to our 2017 Plan pursuant to (a) and (b) is 8,325,000 shares). The number of shares available for issuance under our 2017 Plan will also include an annual increase on the first day of each fiscal year beginning on January 1, 2019, equal to the least of:

- 10,000,000 shares;
- five percent (5%) of the outstanding shares of our common stock as of the last day of the immediately preceding fiscal year; or
- such other amount as our board of directors may determine.

If an award expires or becomes unexercisable without having been exercised in full, is surrendered pursuant to an exchange program, or, with respect to restricted stock, restricted stock units, performance units or performance shares, is forfeited to or repurchased due to failure to vest, the unpurchased shares (or for awards other than stock options or stock appreciation rights, the forfeited or repurchased shares) will become available for future grant or sale under the 2017 Plan. With respect to stock appreciation rights, only the net shares actually issued will cease to be available under the 2017 Plan and all remaining shares under stock appreciation rights will remain available for future grant or sale under the 2017 Plan. Shares that have actually been issued under the 2017 Plan under any award will not be returned to the 2017 Plan; provided, however, that if shares issued pursuant to awards of restricted stock, restricted stock units, performance shares or performance units are repurchased or forfeited, such shares will become available for future grant under the 2017 Plan. Shares used to pay the exercise price of an award or satisfy the tax withholding obligations related to an award will become available for future grant or sale under the 2017 Plan. To the extent an award is paid out in cash rather than shares, such cash payment will not result in a reduction in the number of shares available for issuance under the 2017 Plan.

Plan Administration. The compensation committee of our board of directors will administer our 2017 Plan. In the case of awards intended to qualify as ''performance-based compensation'' within the meaning of Section 162(m) of the Code, the committee will consist of two or more ''outside directors'' within the meaning of Section 162(m) of the Code. In addition, if we determine it is desirable to qualify transactions under our 2017 Plan as exempt under Rule 16b-3 of the Exchange Act, such transactions will be structured to satisfy the requirements for exemption under Rule 16b-3. Subject to the provisions of our 2017 Plan, the administrator has the power to administer our 2017 Plan and make all determinations deemed necessary or advisable for administering the 2017 Plan, including but not

limited to, the power to determine the fair market value of our common stock, select the service providers to whom awards may be granted, determine the number of shares covered by each award, approve forms of award agreements for use under the 2017 Plan, determine the terms and conditions of awards (including, but not limited to, the exercise price, the times or times at which the awards may be exercised, any vesting acceleration or waiver or forfeiture restrictions, and any restriction or limitation regarding any award or the shares relating thereto), construe and interpret the terms of our 2017 Plan and awards granted under it, to prescribe, amend and rescind rules relating to our 2017 Plan, including creating sub-plans, and to modify or amend each award, including but not limited to the discretionary authority to extend the post-termination exercisability period of awards (provided that no option or stock appreciation right will be extended past its original maximum term), and to allow a participant to defer the receipt of payment of cash or the delivery of shares that would otherwise be due to such participant under an award). The administrator also has the authority to allow participants the opportunity to transfer outstanding awards to a financial institution or other person or entity selected by the administrator and to institute an exchange program by which outstanding awards may be surrendered or cancelled in exchange for awards of the same type which may have a higher or lower exercise price and/or different terms, awards of a different type and/or cash, or by which the exercise price of an outstanding award is increased or reduced. The administrator's decisions, interpretations and other actions are final and binding on all participants.

Stock Options. Stock options may be granted under our 2017 Plan. The exercise price of options granted under our 2017 Plan must at least be equal to the fair market value of our common stock on the date of grant. The term of an option may not exceed ten years. With respect to any participant who owns more than 10% of the voting power of all classes of our outstanding stock, the term of an incentive stock option granted to such participant must not exceed five years and the exercise price must equal at least 110% of the fair market value on the grant date. The administrator will determine the methods of payment of the exercise price of an option, which may include cash, shares or other property acceptable to the administrator, as well as other types of consideration permitted by applicable law. After the termination of service of an employee, director or consultant, he or she may exercise his or her option for the period of time stated in his or her option agreement. In the absence of a specified time in an award agreement, if termination is due to death or disability, the option will remain exercisable for 12 months. In all other cases, in the absence of a specified time in an award agreement, the option will remain exercisable for three months following the termination of service. An option may not be exercised later than the expiration of its term. Subject to the provisions of our 2017 Plan, the administrator determines the other terms of options.

Stock Appreciation Rights. Stock appreciation rights may be granted under our 2017 Plan. Stock appreciation rights allow the recipient to receive the appreciation in the fair market value of our common stock between the exercise date and the date of grant. Stock appreciation rights may not have a term exceeding ten years. After the termination of service of an employee, director or consultant, he or she may exercise his or her stock appreciation right for the period of time stated in his or her stock appreciation rights agreement. In the absence of a specified time in an award agreement, if termination is due to death or disability, the stock appreciation rights will remain exercisable for 12 months. In all other cases, in the absence of a specified time in an award agreement, the stock appreciation rights will remain exercisable for three months following the termination of service. However, in no event may a stock appreciation right be exercised later than the expiration of its term. Subject to the provisions of our 2017 Plan, the administrator determines the other terms of stock appreciation rights, including when such rights become exercisable and whether to pay any increased appreciation in cash or with shares of our common stock, or a combination thereof, except that the per share exercise price for the shares to be issued pursuant to the exercise of a stock appreciation right will be no less than 100% of the fair market value per share on the date of grant.

Restricted Stock. Restricted stock may be granted under our 2017 Plan. Restricted stock awards are grants of shares of our common stock that vest in accordance with terms and conditions established by the administrator. The administrator will determine the number of shares of restricted stock granted to any employee, director or consultant and, subject to the provisions of our 2017 Plan, will determine the terms and conditions of such awards. The administrator may impose whatever conditions to vesting it determines to be appropriate (for example, the administrator may set restrictions based on the achievement of specific performance goals or continued service to us); provided, however, that the administrator, in its sole discretion, may accelerate the time at which any restrictions will lapse or be removed. Recipients of restricted stock awards generally will have voting and dividend rights with respect to such shares upon grant without regard to vesting, unless the administrator provides otherwise. Shares of restricted stock that do not vest are subject to our right of repurchase or forfeiture.

RSUs. RSUs may be granted under our 2017 Plan. RSUs are bookkeeping entries representing an amount equal to the fair market value of one share of our common stock. Subject to the provisions of our 2017 Plan, the administrator determines the terms and conditions of RSUs, including the vesting criteria and the form and timing of payment. The administrator may set vesting criteria based upon the achievement of company-wide, divisional, business unit or individual goals (including, but not limited to, continued employment or service), applicable federal or state securities laws or any other basis determined by the administrator in its discretion. The administrator, in its sole discretion, may pay earned restricted stock units in the form of cash, in shares or in some combination thereof. Notwithstanding the foregoing, the administrator, in its sole discretion, may accelerate the time at which any restrictions will lapse or be removed.

Performance Units and Performance Shares. Performance units and performance shares may be granted under our 2017 Plan. Performance units and performance shares are awards that will result in a payment to a participant only if performance goals established by the administrator are achieved or the awards otherwise vest. The administrator will establish performance objectives or other vesting criteria in its discretion, which, depending on the extent to which they are met, will determine the number and/or the value of performance units and performance shares to be paid out to participants. The administrator may set performance objectives based on the achievement of company-wide, divisional, business unit or individual goals (including, but not limited to, continued employment or service), applicable federal or state securities laws or any other basis determined by the administrator in its discretion. After the grant of a performance unit or performance share, the administrator, in its sole discretion, may reduce or waive any performance criteria or other vesting provisions for such performance units or performance shares. Performance units shall have an initial dollar value established by the administrator on or prior to the grant date. Performance shares shall have an initial value equal to the fair market value of our common stock on the grant date. The administrator, in its sole discretion, may pay earned performance units or performance shares in the form of cash, in shares or in some combination thereof.

Outside Directors. Our 2017 Plan provides that all outside (non-employee) directors will be eligible to receive all types of awards (except for incentive stock options) under our 2017 Plan. We have adopted a formal policy pursuant to which our outside directors will be eligible to receive equity awards under our 2017 Plan, and they may also receive discretionary awards not covered by the policy. In order to provide a maximum limit on the awards that can be made to our outside directors, our 2017 Plan provides that in any given fiscal year, an outside director will not be granted awards having a grant-date fair value greater than $1,000,000, but this limit is increased to $1,600,000 in connection with his or her initial service (in each case, excluding awards granted to him or her as a consultant or employee). The grant-date fair values will be determined according to GAAP. The maximum limits do not reflect the intended size of any potential grants or a commitment to make grants to our outside directors under our 2017 Plan in the future.

Non-Transferability of Awards. Unless the administrator provides otherwise, our 2017 Plan generally does not allow for the transfer of awards and only the recipient of an award may exercise an award during his or her lifetime. If the administrator makes an award transferrable, such award will contain such additional terms and conditions as the administrator deems appropriate.

Certain Adjustments. In the event of certain changes in our capitalization, to prevent diminution or enlargement of the benefits or potential benefits available under our 2017 Plan, the administrator will adjust the number and class of shares that may be delivered under our 2017 Plan and/or the number, class and price of shares covered by each outstanding award and the numerical share limits set forth in our 2017 Plan.

Dissolution or Liquidation. In the event of our proposed liquidation or dissolution, the administrator will notify participants as soon as practicable and all awards will terminate immediately prior to the consummation of such proposed transaction.

Merger or Change in Control. Our 2017 Plan provides that in the event of a merger or change in control, as defined under our 2017 Plan, each outstanding award will be treated as the administrator determines, without a participant's consent. The administrator is not required to treat all awards, all awards held by a participant or all awards of the same type, similarly.

In the event that a successor corporation or its parent or subsidiary does not assume or substitute an equivalent award for any outstanding award, then such award will fully vest, all restrictions on such award will lapse, all performance goals or other vesting criteria applicable to such award will be deemed achieved at 100% of target levels and such award will become fully exercisable, if applicable, for a specified period prior to the transaction, unless specifically provided for otherwise under the applicable award agreement or other written agreement with the participant. The award will then terminate upon the expiration of the specified period of time. If an option or stock appreciation right is not assumed or substituted, the administrator will notify the participant in writing or electronically that such option or stock appreciation right will be exercisable for a period of time determined by the administrator in its sole discretion and the option or stock appreciation right will terminate upon the expiration of such period.

If an outside director's awards are assumed or substituted for in a merger or change in control and the service of such outside director is terminated on or following a change in control, other than pursuant to a voluntary resignation, his or her options and stock appreciation rights, if any, will vest fully and become immediately exercisable, all restrictions on his or her restricted stock and restricted stock units will lapse and all performance goals or other vesting requirements for his or her performance shares and units will be deemed achieved at 100% of target levels and all other terms and conditions met.

Amendment; Termination. The administrator has the authority to amend, suspend or terminate our 2017 Plan provided such action does not impair the existing rights of any participant. Our 2017 Plan automatically will terminate in 2027, unless we terminate it sooner.

2017 Employee Stock Purchase Plan

Our board of directors adopted, and our stockholders approved, our 2017 Employee Stock Purchase Plan, or ESPP. Our ESPP became effective on the business day immediately prior to the effective date of the registration statement of which this prospectus forms a part. We believe that allowing our employees to participate in our ESPP provides them with a further incentive towards ensuring our success and accomplishing our corporate goals.

Authorized Shares. A total of 1,000,000 shares of our common stock will be available for sale under our ESPP. The number of shares of our common stock that will be available for sale under our ESPP also includes an annual increase on the first day of each fiscal year beginning on January 1, 2019, equal to the least of:

- 2,000,000 shares;
- one percent (1%) of the outstanding shares of our common stock as of the last day of the immediately preceding fiscal year; or
- such other amount as the administrator may determine.

Plan Administration. The compensation committee of our board of directors will administer our ESPP, and have full but non-exclusive authority to interpret the terms of our ESPP and determine eligibility to participate, subject to the conditions of our ESPP, as described below. The administrator will have full and exclusive discretionary authority to construe, interpret and apply the terms of the ESPP, to delegate ministerial duties to any of our employees, to designate separate offerings under the ESPP, to designate our subsidiaries and affiliates as participating in the ESPP, to determine eligibility, to adjudicate all disputed claims filed under the ESPP and to establish procedures that it deems necessary or advisable for the administration of the ESPP, including, but not limited to, adopting such procedures, sub-plans and appendices to the enrollment agreement as are necessary or appropriate to permit participation in the ESPP by employees who are foreign nationals or employed outside the U.S. The administrator's findings, decisions and determinations are final and binding on all participants to the full extent permitted by law.

Eligibility. Generally, all of our employees will be eligible to participate if they are customarily employed by us, or any participating subsidiary, for at least 20 hours per week and more than five months in any calendar year. The administrator, in its discretion, may, prior to an enrollment date for all options granted on such enrollment date in an offering, determine that an employee who (i) has not completed at least two years of service (or a lesser period of time determined by the administrator) since his or her last hire date, (ii) customarily works not more than 20 hours per week (or a lesser period of time determined by the administrator), (iii) customarily works not more than five months per calendar year (or a lesser period of time determined by the administrator), (iv) is a highly compensated employee within the meaning of Section 414(q) of the Code or (v) is a highly compensated employee within the meaning of Section 414(q) of the Code with compensation above a certain level or is an officer or subject to disclosure requirements under Section 16(a) of the Exchange Act, is or is not eligible to participate in such offering period.

However, an employee may not be granted rights to purchase shares of our common stock under our ESPP if such employee:

- immediately after the grant would own capital stock possessing 5% or more of the total combined voting power or value of all classes of our capital stock; or
- hold rights to purchase shares of our common stock under all of our employee stock purchase plans that accrue at a rate that exceeds $25,000 worth of shares of our common stock for each calendar year.

Offering Periods. Our ESPP includes a component that allows us to make offerings intended to qualify under Section 423 of the Code and a component that allows us to make offerings not intended to qualify under Section 423 of the Code to designated companies, as described in our ESPP. Our 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 and November 30 of each year, except for the first offering period, which will commence on the first trading day on or after the effective date of

the registration statement of which this prospectus forms a part and will end on the first trading day on or after November 30, 2018. Each offering period will include purchase periods, which will be the approximately six-month period commencing with one exercise date and ending with the next exercise date; provided, however, that the first exercise date under the ESPP will be the first trading day on or after May 31, 2018.

Contributions. Our ESPP permits participants to purchase shares of our common stock through contributions (in the form of payroll deductions or otherwise to the extent permitted by the administrator) of up to 15% of their eligible compensation. A participant may purchase a maximum of 2,000 shares of our common stock during a purchase period.

Exercise of Purchase Right. Amounts contributed and accumulated by the participant are used to purchase shares of our common stock at the end of each six-month purchase period. The purchase price of the shares will be 85% of the lower of the fair market value of our common stock on the first trading day of each offering period or on the exercise date. If the fair market value of our common stock on the exercise date is less than the fair market value on the first trading day of the offering period, participants will be withdrawn from the current offering period following their purchase of shares of our common stock on the purchase date and will be automatically re-enrolled in a new offering period. Participants may end their participation at any time during an offering period and will be paid their accrued contributions that have not yet been used to purchase shares of our common stock. Participation ends automatically upon termination of employment with us.

Non-Transferability. A participant may not transfer rights granted under our ESPP. If our compensation committee permits the transfer of rights, it may only be done by will, the laws of descent and distribution or as otherwise provided under our ESPP.

Merger or Change in Control. Our ESPP provides that in the event of a merger or change in control, as defined under our ESPP, a successor corporation may assume or substitute each outstanding purchase right. If the successor corporation refuses to assume or substitute for the outstanding purchase right, the offering period then in progress will be shortened, and a new exercise date will be set that will be before the date of the proposed merger or change in control. The administrator will notify each participant that the exercise date has been changed and that the participant's option will be exercised automatically on the new exercise date unless prior to such date the participant has withdrawn from the offering period.

Amendment; Termination. The administrator has the authority to amend, suspend or terminate our ESPP, except that, subject to certain exceptions described in our ESPP, no such action may adversely affect any outstanding rights to purchase shares of our common stock under our ESPP. Our ESPP automatically will terminate in 2037, unless we terminate it sooner.

2015 Stock Incentive Plan

On April 21, 2015, our board of directors adopted and our stockholders approved our 2015 Plan. The 2015 Plan has been amended from time to time to increase the aggregate number of shares of our common stock reserved for issuance under the 2015 Plan, and was most recently amended on November 11, 2016, which amendment was approved by our stockholders on December 12, 2016. The 2015 Plan permits the grant of incentive stock options, within the meaning of Section 422 of the Code, to our employees and the employees of any parent and subsidiary corporation or other entities the employees of which are eligible to receive incentive stock options under the Code, and for the grant of nonstatutory stock options, stock appreciation rights, restricted stock awards, restricted stock units and other stock-based awards to our employees, officers, directors, consultants and advisors or any parent or subsidiary of ours. It is expected that as of one business day prior to the effectiveness of the

registration statement of which this prospectus forms a part, the 2015 Plan will be terminated and we will not grant any additional awards under the 2015 Plan thereafter. However, the 2015 Plan will continue to govern the terms and conditions of the outstanding awards previously granted thereunder.

Authorized Shares. The maximum aggregate number of shares issuable under the 2015 Plan was 8,325,000 shares of our common stock. As of September 30, 2017, options to purchase 6,179,687 shares of our common stock were outstanding under the 2015 Plan, 505,731 shares of restricted stock were outstanding under the 2015 Plan, no shares subject to stock appreciation rights were outstanding under the 2015 Plan, no restricted stock units were outstanding under the 2015 Plan and no other stock-based awards were outstanding under the 2015 Plan.

Plan Administration. Our board of directors or a committee or subcommittee delegated by our board of directors administers the 2015 Plan. Subject to the provisions of the 2015 Plan, the administrator has the authority to grant awards and to adopt, amend and repeal such administrative rules, guidelines and practices relating to the 2015 Plan as it deems advisable, including to establish one or more sub-plans for purposes of satisfying applicable securities, tax or other laws of various jurisdictions. The administrator may amend or terminate any outstanding award, including substituting an award for another award of the same or a different type, changing the date of exercise or realization and converting an incentive stock option into a nonstatutory stock option, although the affected participant's consent will be required unless the administrator determines that the action does not materially adversely affect the participant's rights under the 2015 Plan, or the change is permitted under the adjustment, merger or Reorganization Event provisions of the 2015 Plan. The administrator may also amend any outstanding award granted under the 2015 Plan to provide an exercise price per share that is lower than the then-current exercise price per share of the outstanding award, and may cancel any outstanding award (whether or not granted under the 2015 Plan) and grant new, substitute awards under the 2015 Plan covering the same or a different number of shares and having an exercise price per share that is lower than the then-current exercise price per share of the cancelled award. The administrator may correct any defect, supply any omission or reconcile any inconsistency in the 2015 Plan or award in the manner and to the extent it deems expedient to carry the 2015 Plan into effect and is the sole and final judge of such expediency. All decisions by the administrator are made in the administrator's sole discretion and are final and binding on all persons having or claiming any interest in the 2015 Plan or in any award.

Stock Options. Stock options may be granted under our 2015 Plan. The exercise price of options granted under our 2015 Plan must at least be equal to 100% of the fair market value of our common stock on the date of grant. The term of a stock option may not exceed 10 years. The administrator will determine the methods of payment of the exercise price of an option, which may include cash or check, owned shares, a broker-assisted cashless exercise, "net exercise," a promissory note, as well as other types of consideration permitted by applicable law.

If a participant's service terminates other than for cause or the participant's death or disability, the participant may exercise his or her option within at least 30 days of termination or such longer period as reflected in the individual award agreement. If a participant's service terminates due to the participant's death or disability, the participant may exercise his or her option within at least six months of termination or such longer period as reflected in the individual award agreement. However, in no event may an option be exercised later than the expiration of its term. Subject to the provisions of the 2015 Plan, the administrator determines the other terms of options.

Stock Appreciation Rights. Stock appreciation rights may be granted under our 2015 Plan. Stock appreciation rights allow the recipient to receive the appreciation in the fair market value of our common stock between the exercise date and the date of grant. Stock appreciation rights may not

have a term exceeding 10 years. After the termination of service of an employee, director or consultant, he or she may exercise his or her stock appreciation right for the period of time stated in his or her stock appreciation right agreement. However, in no event may a stock appreciation right be exercised later than the expiration of its term. Subject to the provisions of our 2015 Plan, the administrator determines the other terms of stock appreciation rights, including when such rights become exercisable and whether to pay any increased appreciation in cash or with shares of our common stock, or a combination thereof, except that the per share measurement price for the shares to be issued pursuant to the exercise of a stock appreciation right will be no less than 100% of the fair market value per share on the date of grant.

Restricted Stock. Restricted stock may be granted under our 2015 Plan. Restricted stock awards are grants of shares of our common stock that vest in accordance with terms and conditions established by the administrator. The administrator will determine the number of shares of restricted stock granted to any employee, director or consultant and, subject to the provisions of our 2015 Plan, will determine the terms and conditions of such awards. The administrator may impose whatever conditions for lapse of the restriction on the shares it determines to be appropriate. Unless otherwise provided in the applicable award agreement, any dividends declared and paid by us with respect to shares of restricted stock will be paid to the participant only if and when such shares become free from the restrictions on transferability and forfeitability that apply to such shares. Shares of restricted stock as to which the restrictions have not lapsed are subject to our right of repurchase or forfeiture.

Restricted Stock Units. Restricted stock units may be granted under our 2015 Plan. Restricted stock units are bookkeeping entries representing an amount equal to the fair market value of one share of our common stock. Subject to the provisions of our 2015 Plan, the administrator will determine the terms and conditions of restricted stock units, including the vesting criteria and the form and timing of payment. The administrator, in its sole discretion, may pay earned restricted stock units in the form of cash, in shares or in some combination thereof. Participants who receive restricted stock units have no voting rights with respect to the restricted stock units. The award agreement for restricted stock units may provide participants with the right to receive an amount equal to any dividends or other distributions declared and paid on an equal number of outstanding shares of our common stock, which may be settled in cash and/or shares, and may be subject to the same restrictions on transfer and forfeitability as the restricted stock units to which they relate, as may be provided in the award agreement.

Other Stock-Based Awards. Other stock based awards may be granted under our 2015 Plan. Other stock-based awards are also available as a form of payment in the settlement of other awards granted under our 2015 Plan or as payment in lieu of compensation to which a participant is otherwise entitled. Other stock-based awards may be paid in shares of our common stock or cash, as determined by the administrator. Subject to the provisions of the 2015 Plan, the administrator determines the terms and conditions of other stock-based awards granted under the 2015 Plan.

Non-Transferability of Awards. Our 2015 Plan generally does not allow for the transfer of awards and only the recipient of an award may exercise an award during his or her lifetime. However, awards that are not subject to Section 409A of the Code may be transferred to family members through gifts or (other than incentive stock options) domestic relations orders, or to an executor or guardian upon the death of a participant.

Certain Adjustments. In the event of certain changes in our capitalization, the administrator will adjust the number and class of shares that may be delivered under the 2015 Plan and/or the number, class, price, repurchase price and other per-share-related provisions, as applicable, of shares covered by, each outstanding award.

Merger or Reorganization Event. The 2015 Plan provides that in the event of a merger or other Reorganization Event, as defined under the 2015 Plan, each outstanding award, except restricted stock, will be treated as the administrator determines, including, without limitation, that awards shall be assumed or substituted, that, upon written notice to a participant; that awards will terminate immediately prior to the consummation of the transaction; that awards will become fully exercisable or restrictions applicable to the award will lapse in whole or in part upon the transaction; or, upon a Reorganization Event under which the holders of shares of common stock will receive a cash payment for each share surrendered in the Reorganization Event, that awards will be terminated in exchange for a cash payment equal to the number of shares subject to the award multiplied by the acquisition price minus the exercise, measurement, or purchase price of the award. In addition, in the event of a Reorganization Event that is a liquidation or dissolution, the administrator may provide that awards will be converted into the right to receive liquidation proceeds (if applicable, net of the exercise, measurement, or purchase price thereof and applicable tax withholdings). Certain additional restrictions apply to restricted stock units to which Section 409A of the Code apply. On a Reorganization Event, our repurchase rights with respect to restricted stock will inure to the benefit of the successor and shall, unless the administrator determines otherwise, apply to the property into which the shares are converted. In the event of our proposed liquidation or dissolution, restrictions on restricted stock then outstanding will be automatically deemed satisfied.

Amendment, Termination. The administrator has the authority to amend the 2015 Plan, provided that if at any time the approval of our stockholders is required as to any modification or amendment under Section 422 of the Code or any successor provision with respect to incentive stock options, our board of directors may not effect such modification or amendment without such approval. As noted above our 2015 Plan will terminate in connection with our adoption of our 2017 Plan and no further awards will be granted thereunder. All outstanding awards will continue to be governed by their existing terms.

Executive Incentive Compensation Plan

In November 2017, our board of directors adopted our Executive Incentive Compensation Plan, or our Incentive Compensation Plan. Our Incentive Compensation Plan allows our compensation committee to provide incentive awards, generally payable in cash, to employees selected by our compensation committee, including our named executive officers, based upon performance goals established by our compensation committee.

Under our Incentive Compensation Plan, our compensation committee determines the performance goals applicable to any award, which goals may include, without limitation, goals related to research and development, regulatory milestones or regulatory-related goals, gross margin, financial milestones, new product or business development, operation margin, product release timelines or other product release milestones, publications, cash flow, procurement, savings, internal structure, leadership development, project, function or portfolio-specific milestones, license or research collaboration agreements, capital raising, initial public offering preparations, patentability and individual objectives such as peer reviews or other subjective or objective criteria. The performance goals may differ from participant to participant and from award to award.

Our compensation committee will administer our Incentive Compensation Plan. The administrator of our Incentive Compensation Plan may, in its sole discretion and at any time, increase, reduce or eliminate a participant's actual award, and/or increase, reduce or eliminate the amount allocated to the bonus pool for a particular performance period. The actual award may be below, at or above a participant's target award, in the discretion of the administrator. The administrator may determine the amount of any reduction on the basis of such factors as it deems relevant, and it is not required to establish any allocation or weighting with respect to the factors it considers.

Actual awards will be paid in cash (or its equivalent) only after they are earned, and, unless otherwise determined by the administrator, a participant must be employed by us through the date the actual award is paid. The compensation committee reserves the right to settle an actual award with a grant of an equity award under our then-current equity compensation plan, which equity award may have such terms and conditions, including vesting, as the compensation committee determines. Payment of awards occurs as soon as administratively practicable after they are earned, but no later than the dates set forth in our Incentive Compensation Plan.

Our board of directors and our compensation committee will have the authority to amend, alter, suspend or terminate our Incentive Compensation Plan, provided such action does not impair the existing rights of any participant with respect to any earned awards.

401(k) Plan

We maintain a 401(k) retirement savings plan for the benefit of our employees, including our named executive officers, who satisfy certain eligibility requirements. Under the 401(k) plan, eligible employees may elect to defer a portion of their compensation, within the limits prescribed by the Code, on a pre-tax or after-tax (Roth) basis through contributions to the 401(k) plan. The 401(k) plan authorizes employer safe harbor contributions. The 401(k) plan is intended to qualify under Sections 401(a) and 501(a) of the Code. As a tax-qualified retirement plan, pre-tax contributions to the 401(k) plan and earnings on those pre-tax contributions are not taxable to the employees until distributed from the 401(k) plan, and earnings on Roth contributions are not taxable when distributed from the 401(k) plan.

CERTAIN RELATIONSHIPS AND RELATED PARTY TRANSACTIONS

In addition to the compensation arrangements, including employment, termination of employment and change in control arrangements, with our directors and executive officers, including those discussed in the sections titled "Management" and "Executive Compensation," and the registration rights described in the section titled "Description of Capital Stock—Registration Rights," the following is a description of each transaction since January 1, 2014 and each currently proposed transaction in which:

- we have been or are to be a participant;
- the amount involved exceeded or exceeds $120,000; and
- any of our directors, executive officers or holders of more than 5% of our outstanding capital stock, or any immediate family member of, or person sharing the household with, any of these individuals or entities, had or will have a direct or indirect material interest.

Sales of Securities

Common stock

From March 2015 through August 2015, we sold an aggregate of 2,815,787 shares of our common stock at a purchase price of $0.04 per share, for an aggregate purchase price of $0.1 million, to six accredited investors and we issued an aggregate of 3,339,043 shares of our common stock at $0.04 to $0.68 per share, with an aggregate fair market value of $0.4 million, to four of our directors, each an accredited investor, in exchange for services to us. The following table summarizes purchases of our common stock by related persons:

Stockholder	Affiliated Director(s) or Officer(s)	Shares of Common Stock	Total Purchase Price
5% Stockholders:			
Entities associated with AKDL, L.P.(1)		312,500	$ 12,500
ARCH Venture Fund VIII, L.P.	Robert Nelsen	312,500	$ 12,500
Flagship Ventures Fund V, L.P.	Douglas Cole, M.D.	312,500	$ 12,500
Entities associated with F-Prime Capital Partners Healthcare Fund IV L.P.(2)	Stephen Knight, M.D.; Stacie Weninger, Ph.D(3)	1,812,499	$ 72,500
Directors and Executive Officers:			
Marc Tessier-Lavigne, Ph.D.		3,114,043	$ 367,550
Vicki Sato, Ph.D.		75,000	$ 3,000
Jay Flatley		75,000	$ 3,000
David Schenkein, M.D.		75,000	$ 3,000

(1) Entities associated with AKDL, L.P. holding our securities whose shares are aggregated for purposes of reporting share ownership information are AKDL, L.P. and Neuro Line Partners, L.P.

(2) Entities associated with F-Prime Capital Partners Healthcare Fund IV L.P. holding our securities whose shares are aggregated for purposes of reporting share ownership information are Impresa Fund III Limited Partnership, F-Prime Capital Partners Healthcare Fund IV L.P. (f/k/a Beacon Bioventures Fund IV Limited Partnership), F-Prime Capital Partners Healthcare Advisors Fund IV LP and F-Prime Capital (f/k/a Fidelity Biosciences Corp.).

(3) Each of Drs. Knight and Weninger resigned as members of our board of directors on August 11, 2017.

Series A-1 Convertible Preferred Stock

In May 2015, we issued and sold an aggregate of 9,777,055 shares of our Series A-1 convertible preferred stock at a purchase price of $4.00 per share, for aggregate proceeds of $39.1 million, to a total of 30 accredited investors.

In July 2015, we issued and sold an aggregate of 2,420,825 shares of our Series A-1 convertible preferred stock at a purchase price of $4.00 per share, for aggregate proceeds of $9.7 million, to a total of 11 accredited investors.

In January 2016, we issued and sold an aggregate of 11,749,997 shares of our Series A-1 convertible preferred stock at a purchase price of $4.00 per share, for aggregate proceeds of $47.0 million, to a total of nine accredited investors.

In June 2016, we issued and sold an aggregate of 22,166,546 shares of our Series A-1 convertible preferred stock at a purchase price of $4.00 per share, for aggregate proceeds of $88.7 million, to a total of eight accredited investors. The following table summarizes purchases of our Series A-1 convertible preferred stock by related persons:

Stockholder	Affiliated Director(s) or Officer(s)	Shares of Series A-1 Convertible Preferred Stock	Total Purchase Price
5% Stockholders:			
Entities associated with AKDL, L.P.(1)		15,243,598	$ 60,974,400
ARCH Venture Fund VIII, L.P.	Robert Nelsen	10,068,749	$ 40,275,000
Flagship Ventures Fund V, L.P.	Douglas Cole, M.D.	8,324,999	$ 33,300,000
Entities associated with F-Prime Capital Partners Healthcare Fund IV L.P.(2)	Stephen Knight, M.D.; Stacie Weninger, Ph.D.(7)	4,468,003	$ 17,872,000
Entities associated with FIL Limited(3)		1,606,995	$ 6,428,000
Executive Officers and Directors:			
Steve E. Krognes(4)		500,000	$ 2,000,000
Vicki Sato, Ph.D.		62,500	$ 250,000
Jay Flatley(5)		250,000	$ 1,000,000
David Schenkein, M.D.(6)		250,000	$ 1,000,000
Marc Tessier-Lavigne, Ph.D.		25,000	$ 100,000

(1) Entities associated with AKDL, L.P. holding our securities whose shares are aggregated for purposes of reporting share ownership information are AKDL, L.P. and Neuro Line Partners, L.P.

(2) Entities associated with F-Prime Capital Partners Healthcare Fund IV L.P. holding our securities whose shares are aggregated for purposes of reporting share ownership information are Impresa Fund III Limited Partnership, F-Prime Capital Partners Healthcare Fund IV L.P. (f/k/a Beacon Bioventures Fund IV Limited Partnership), F-Prime Capital Partners Healthcare Advisors Fund IV LP and F-Prime Capital (f/k/a Fidelity Biosciences Corp.).

(3) Entities associated with FIL Limited holding our securities whose shares are aggregated for purposes of reporting share ownership information are FIL Limited, Asia Ventures III L.P., Japan Ventures I L.P., FIL Capital Investments (Mauritius) II Limited, Asia Partners III LP, Japan Partners I LP and India Partners II LP.

(4) Consists of 500,000 shares of Series A-1 convertible preferred stock held of record by The Steve Edward Krognes Revocable Trust, for which Mr. Krognes serves as trustee.

(5) Consists of 250,000 shares of Series A-1 convertible preferred stock held by The Flatley Family Trust, for which Mr. Flatley serves as trustee.

(6) Consists of (a) 116,011 shares of Series A-1 convertible preferred stock held by the David P. Schenkein 2015 Denali Qualified Annuity Trust, for which Dr. Schenkein serves as trustee,

(b) 8,988 shares of Series A-1 convertible preferred stock held by the David P. Schenkein 2004 Revocable Trust, for which Dr. Schenkein serves as trustee, (c) 116,011 shares of Series A-1 convertible preferred stock held by the Amy P. Schenkein 2015 Denali Qualified Annuity Trust and (d) 8,988 shares of Series A-1 convertible preferred stock held by the Amy P. Schenkein 2004 Revocable Trust. Dr. Schenkein shares voting and dispositive power over the shares held by the Amy P. Schenkein 2015 Denali Qualified Annuity Trust and the Amy P. Schenkein 2004 Revocable Trust.

(7) Each of Drs. Knight and Weninger resigned as members of our board of directors on August 11, 2017.

Series A-2 Convertible Preferred Stock

In June 2016, we issued and sold an aggregate of 4,361,527 shares of our Series A-2 convertible preferred stock at a purchase price of $8.00 per share, for aggregate proceeds of $34.9 million, to a total of 15 accredited investors. The following table summarizes purchases of our Series A-2 convertible preferred stock by related persons:

Stockholder	Affiliated Director(s) or Officer(s)	Shares of Series A-2 Convertible Preferred Stock	Total Purchase Price
5% Stockholders:			
Entities associated with AKDL, L.P.(1)		2,628,200	$ 21,025,600
ARCH Venture Fund VIII, L.P.	Robert Nelsen	375,000	$ 3,000,000
Flagship Ventures Fund V, L.P.	Douglas Cole, M.D.	125,000	$ 1,000,000
Entities associated with F-Prime Capital Partners Healthcare Fund IV L.P.(2)	Stephen Knight, M.D.; Stacie Weninger, Ph.D.(4)	83,123	$ 664,990
Entities associated with FIL Limited(3)		41,876	$ 335,010

(1) Entities associated with AKDL, L.P. holding our securities whose shares are aggregated for purposes of reporting share ownership information are AKDL, L.P. and Neuro Line Partners, L.P.

(2) Entities associated with F-Prime Capital Partners Healthcare Fund IV L.P. holding our securities whose shares are aggregated for purposes of reporting share ownership information are Impresa Fund III Limited Partnership, F-Prime Capital Partners Healthcare Fund IV L.P. (f/k/a Beacon Bioventures Fund IV Limited Partnership), F-Prime Capital Partners Healthcare Advisors Fund IV LP and F-Prime Capital (f/k/a Fidelity Biosciences Corp.).

(3) Entities associated with FIL Limited holding our securities whose shares are aggregated for purposes of reporting share ownership information are FIL Limited, Asia Ventures III L.P., Japan Ventures I L.P., FIL Capital Investments (Mauritius) II Limited, Asia Partners III LP, Japan Partners I LP and India Partners II LP.

(4) Each of Drs. Knight and Weninger resigned as members of our board of directors on August 11, 2017.

Series B-1 Convertible Preferred Stock

In June 2016, we issued and sold an aggregate of 7,646,241 shares of our Series B-1 convertible preferred stock at a purchase price of $16.00 per share, for aggregate proceeds of $122.3 million, to a total of 17 accredited investors.

In August 2016, we issued and sold an aggregate of 478,124 shares of our Series B-1 convertible preferred stock at a purchase price of $16.00 per share, for aggregate proceeds of $7.7 million, to a total of 10 accredited investors. The following table summarizes purchases of our Series B-1 convertible preferred stock by related persons:

Stockholder	Affiliated Director(s) or Officer(s)	Shares of Series B-1 Convertible Preferred Stock	Total Purchase Price
5% Stockholders:			
Entities associated with AKDL, L.P.(1)		2,115,000	$33,840,000
ARCH Venture Fund VIII, L.P.	Robert Nelsen	312,500	$ 5,000,000
Flagship Ventures Fund V, L.P.	Douglas Cole, M.D.	156,250	$ 2,500,000
Entities associated with F-Prime Capital Partners Healthcare Fund IV L.P.(2)	Stephen Knight, M.D.; Stacie Weninger, Ph.D.(4)	207,809	$ 3,325,000
Entities associated with FIL Limited(3)		104,690	$ 1,675,000
Executive Officers and Directors:			
Ryan J. Watts, Ph.D.		12,500	$ 200,000

(1) Entities associated with AKDL, L.P. holding our securities whose shares are aggregated for purposes of reporting share ownership information are AKDL, L.P. and Neuro Line Partners, L.P.

(2) Entities associated with F-Prime Capital Partners Healthcare Fund IV L.P. holding our securities whose shares are aggregated for purposes of reporting share ownership information are Impresa Fund III Limited Partnership, F-Prime Capital Partners Healthcare Fund IV L.P. (f/k/a Beacon Bioventures Fund IV Limited Partnership), F-Prime Capital Partners Healthcare Advisors Fund IV LP and F-Prime Capital (f/k/a Fidelity Biosciences Corp.).

(3) Entities associated with FIL Limited holding our securities whose shares are aggregated for purposes of reporting share ownership information are FIL Limited, Asia Ventures III L.P., Japan Ventures I L.P., FIL Capital Investments (Mauritius) II Limited, Asia Partners III LP, Japan Partners I LP and India Partners II LP.

(4) Each of Drs. Knight and Weninger resigned as members of our board of directors on August 11, 2017.

Investors' Rights Agreement

We are party to an investors' rights agreement, as amended, with certain holders of our capital stock, including Ryan J. Watts, Ph.D., Alexander O. Schuth, M.D., Marc Tessier-Lavigne, Ph.D., Jay Flatley, Vicki Sato, Ph.D., David Schenkein, M.D., entities associated with AKDL, L.P., ARCH Venture Fund VIII, L.P., an entity affiliated with Robert Nelsen, entities associated with F-Prime Capital Partners Healthcare Fund IV L.P., entities associated with FIL Limited and Flagship Ventures Fund V, L.P., an entity affiliated with Douglas Cole, M.D. Under our investors' rights agreement, certain holders of our capital stock have the right to demand that we file a registration statement or request that their shares of our capital stock be covered by a registration statement that we are otherwise filing. See the section titled "Description of Capital Stock—Registration Rights" for additional information regarding these registration rights.

Right of First Refusal and Co-Sale Agreement

Pursuant to our equity compensation plans and certain agreements with certain holders of our capital stock, including Ryan J. Watts, Ph.D., Alexander O. Schuth, M.D., Steve E. Krognes, Marc Tessier-Lavigne, Ph.D., Jay Flatley, Vicki Sato, Ph.D., David Schenkein, M.D., entities associated with AKDL, L.P., ARCH Venture Fund VIII, L.P., an entity affiliated with Robert Nelsen, entities associated with F-Prime Capital Partners Healthcare Fund IV L.P., entities associated with FIL Limited and Flagship Ventures Fund V, L.P., an entity affiliated with Douglas Cole, M.D., including a right of first

refusal and co-sale agreement, as amended, we or our assignees have a right to purchase shares of our common stock which stockholders propose to sell to other parties. This right will terminate upon the completion of this offering. See the section titled “Principal Stockholders” for additional information regarding beneficial ownership of our capital stock.

Voting Agreement

We are party to a voting agreement, as amended under which certain holders of our capital stock, including Ryan J. Watts, Ph.D., Alexander O. Schuth, M.D., Steve E. Krognes, Marc Tessier-Lavigne, Ph.D., Jay Flatley, Vicki Sato, Ph.D., David Schenkein, M.D., entities associated with AKDL, L.P., ARCH Venture Fund VIII, L.P., an entity affiliated with Robert Nelsen, entities associated with F-Prime Capital Partners Healthcare Fund IV L.P., entities associated with FIL Limited and Flagship Ventures Fund V, L.P., an entity affiliated with Douglas Cole, M.D., have agreed as to the manner in which they will vote their shares of our capital stock on certain matters, including with respect to the election of directors. This agreement will terminate upon the completion of this offering, and thereafter none of our stockholders will have any special rights regarding the election or designation of members of our board of directors after the completion of this offering.

Indemnification Agreements

We have entered, and intend to continue to enter, into separate indemnification agreements with each of our directors and executive officers, in addition to the indemnification that will be provided for in our amended and restated certificate of incorporation and amended and restated bylaws. The indemnification agreements and our amended restated certificate of incorporation and amended and restated bylaws that will be in effect upon the completion of this offering require us to indemnify our directors, executive officers and certain controlling persons to the fullest extent permitted by Delaware law. See the section titled “Executive Compensation—Limitation of Liability and Indemnification” for additional information.

Participation in this Offering

Certain of our existing stockholders, including one that beneficially owns more than 5% of our outstanding common stock, have agreed to purchase approximately 5,300,000 shares of our common stock in this offering at the initial public offering price.

Related Party Transaction Policy

Our audit committee will have the primary responsibility for reviewing and approving or disapproving “related party transactions,” which are transactions between us and related persons in which the aggregate amount involved exceeds or may be expected to exceed $120,000 and in which a related person has or will have a direct or indirect material interest. The written charter of our audit committee will provide that our audit committee shall review and approve in advance any related party transaction.

We have adopted a formal written policy providing that we are not permitted to enter into any transaction that exceeds $120,000 and in which any related person has a direct or indirect material interest without the consent of our audit committee. In approving or rejecting any such transaction, our audit committee is to consider the relevant facts and circumstances available and deemed relevant to our audit committee, including whether the transaction is on terms no less favorable than terms generally available to an unaffiliated third party under the same or similar circumstances and the extent of the related person’s interest in the transaction.

PRINCIPAL STOCKHOLDERS

The following table sets forth the beneficial ownership of our common stock as of November 24, 2017 by:

- each person, or group of affiliated persons, who is known by us to beneficially own more than 5% of our common stock;
- each of the named executive officers;
- each of our directors; and
- all of our current executive officers and directors as a group.

We have determined beneficial ownership in accordance with the rules of the SEC, and thus it represents sole or shared voting or investment power with respect to our securities. Unless otherwise indicated below, to our knowledge, the persons and entities named in the table have sole voting and sole investment power with respect to all shares that they beneficially owned, subject to community property laws where applicable. The information does not necessarily indicate beneficial ownership for any other purpose, including for purposes of Sections 13(d) and 13(g) of the Exchange Act.

Certain of our existing stockholders, including one that beneficially owns more than 5% of our outstanding common stock, have agreed to purchase approximately 5,300,000 shares of our common stock in this offering at the initial public offering price.

We have based our calculation of the percentage of beneficial ownership prior to this offering on 74,090,587 shares of our common stock outstanding as of November 24, 2017, which includes 60,365,020 shares of our common stock resulting from the conversion of all outstanding shares of our convertible preferred stock (including our Series B-2 convertible preferred stock issued in November 2017) into our common stock immediately prior to the completion of this offering, as if this conversion had occurred as of November 24, 2017. We have based our calculation of the percentage of beneficial ownership after this offering on 87,979,475 shares of our common stock outstanding immediately after the completion of this offering, assuming no exercise by the underwriters of their option to purchase additional shares. We have deemed shares of our common stock subject to stock options that are currently exercisable or exercisable within 60 days of November 24, 2017, to be outstanding and to be beneficially owned by the person holding the stock option for the purpose of computing the percentage ownership of that person. We did not deem these shares outstanding, however, for the purpose of computing the percentage ownership of any other person.

Unless otherwise indicated, the address of each beneficial owner listed in the table below is c/o Denali Therapeutics Inc., 151 Oyster Point Blvd., 2nd Floor, South San Francisco, CA 94080.

	Shares Beneficially Owned Prior to this Offering		Shares Beneficially Owned After this Offering	
Name of Beneficial Owner	Shares	Percentage	Shares	Percentage
5% Stockholders:				
Entities associated with AKDL, L.P. (1)	20,299,298	27.4%	20,574,298	23.4%
ARCH Venture Fund VIII, L.P. (2)	11,068,749	14.9%	11,068,749	12.6%
Flagship Ventures Fund V, L.P. (3)	8,918,749	12.0%	8,918,749	10.1%
Entities associated with F-Prime Capital Partners Healthcare Fund IV L.P. (4)	4,889,994	6.6%	4,889,994	5.6%
Entities associated with FIL Limited (5)	4,184,982	5.6%	4,184,982	4.8%
Named Executive Officers and Directors:				
Ryan J. Watts, Ph.D. (6)	2,815,138	3.8%	2,815,138	3.2%
Alexander O. Schuth, M.D. (7)	810,089	1.1%	810,089	*
Steve E. Krognes (8)	1,000,000	1.3%	1,000,000	1.1%
Carole Ho, M.D. (9)	484,375	*	484,375	*
Vicki Sato, Ph.D. (10)	150,000	*	150,000	*
Douglas Cole, M.D. (11)	—	—	—	—
Jay Flatley (12)	325,000	*	325,000	*
Robert Nelsen (13)	11,068,749	14.9%	11,068,749	12.6%
David Schenkein, M.D. (14)	324,998	*	324,998	*
Marc Tessier-Lavigne, Ph.D. (15)	3,139,043	4.2%	3,139,043	3.6%
All executive officers and directors as a group (10 persons) (16)	20,117,392	27.0%	20,117,392	22.8%

* Represents beneficial ownership of less than one percent (1%) of the outstanding shares of our common stock.

(1) Consists of (a) 19,187,499 shares held of record by AKDL, L.P., (b) 1,111,799 shares held of record by Neuro Line Partners, L.P. and (c) 275,000 shares AKDL, L.P. agreed to purchase in this offering. Crestline SI (GP), L.P., or Crestline SI, is the general partner of AKDL, L.P. and Crestline Investors, Inc., or Crestline, is the general partner of Crestline SI. Bratton Capital Management, L.P. is the general partner of Neuro Line Partners, L.P. and Bratton Capital, Inc. is the general partner of Bratton Capital Management, L.P. Douglas K. Bratton, as the sole director of Crestline and Bratton Capital, Inc., has sole voting and investment control with respect to the shares held by AKDL, L.P. and Neuro Line Partners, L.P. The address of these entities is 201 Main Street, Suite 1900, Fort Worth, TX 76102.

(2) Consists of 11,068,749 shares held of record by ARCH Venture Fund VIII, L.P., or ARCH Venture Fund VIII. ARCH Venture Partners VIII, L.P., or AVP VIII LP, as the sole general partner of ARCH Venture Fund VIII, may be deemed to beneficially own certain of the shares held by ARCH Venture Fund VIII. AVP VIII LP disclaims beneficial ownership of all shares held by ARCH Venture Fund VIII in which AVP VIII LP does not have an actual pecuniary interest. ARCH Venture Partners VIII, LLC, or AVP VIII LLC, as the sole general partner of AVP VIII LP, may be deemed to beneficially own certain of the shares held by ARCH Venture Fund VIII. AVP VIII LLC disclaims beneficial ownership of all shares held by ARCH Venture Fund VIII in which AVP VIII LLC does not have an actual pecuniary interest. As the managing directors of AVP VIII LLC, Keith Crandell, Robert Nelsen, one of our directors, and Clinton Bybee (collectively, the Managing Directors), share voting and investment control with respect to the shares held by ARCH Venture Fund VIII. The Managing Directors disclaim beneficial ownership of all shares held by ARCH Venture Fund VIII except to the extent of any pecuniary interest therein. The address of these entities is 8755 West Higgins Road, Suite 1025, Chicago, IL 60631.

(3) Consists of 8,918,749 shares held of record by Flagship Ventures Fund V, L.P., or Flagship V. Flagship Ventures Fund V General Partner LLC, or Flagship V GP, is the general partner of Flagship V. As the manager of Flagship V GP, Noubar B. Afeyan, Ph.D. has sole voting and investment control with respect to the shares held by Flagship V. In addition, Dr. Cole, a member of our board of directors, is a member of Flagship V GP but does not have voting or investment control with respect to the shares held by Flagship V. Dr. Cole disclaims beneficial ownership of all shares held by Flagship V. The address of these entities is 55 Cambridge Parkway, Suite 800E, Cambridge, MA 02142.

(4) Consists of (a) 2,999,521 shares held of record by Impresa Fund III Limited Partnership, (b) 1,107,257 shares held of record by F-Prime Capital Partners Healthcare Fund IV LP (f/k/a Beacon Bioventures Fund IV Limited Partnership), (c) 33,215 shares held of record by F-Prime Capital Partners Healthcare Advisors Fund IV LP, and (d) 750,001 shares held of record by F-Prime Inc. (f/k/a Fidelity Biosciences Corp.) (collectively, the Entities

associated with F-Prime Capital Partners Healthcare Fund IV LP). The general partner of F-Prime Capital Partners Healthcare Fund IV LP is F-Prime Capital Partners Healthcare Advisors Fund IV LP. F-Prime Capital Partners Healthcare Advisors Fund IV LP is solely managed by Impresa Management LLC, the general partner of its general partner and its investment manager. Impresa Management LLC is owned, directly or indirectly, by various shareholders and employees of FMR LLC. The general partner of Impresa Fund III Limited Partnership is Impresa Management LLC. F-Prime Inc. is a wholly-owned subsidiary of FMR LLC. Each of the entities listed above expressly disclaims beneficial ownership of the securities listed above except to the extent of any pecuniary interest therein. The address of these entities is 245 Summer Street, Boston, MA 02210.

(5) Consists of (a) 1,914,833 shares held of record by FIL Limited, (b) 1,460,570 shares held of record by Asia Ventures III L.P., (c) 401,692 shares held of record by Japan Ventures I L.P., (d) 400,456 shares held of record by FIL Capital Investments (Mauritius) II Limited, (e) 5,146 shares held of record by Asia Partners III LP, (f) 906 shares held of record by Japan Partners I LP and (g) 1,379 shares held of record by India Partners II LP (collectively, the Entities associated with FIL Limited). The general partner of Asia Ventures III L.P. is Asia Partners III LP. The general partner of Japan Ventures I L.P. is Japan Partners I LP. The general partner of Asia Partners III LP is FIL Capital Management Ltd. The general partner of Japan Partners I LP is FIL Capital Management Ltd. The general partner of India Partners II LP is FIL Capital Management Ltd. Each of the entities listed above expressly disclaims beneficial ownership of the securities listed above except to the extent of any pecuniary interest therein. The address of each of these entities except for FIL Capital Investments (Mauritius) II Limited is Pembroke Hall, 42 Crow Lange, Pembroke, Bermuda HM 19. The address of FIL Capital Investments (Mauritius) II Limited is c/o Cim Fund Services Ltd, 33 Edith Cavell Street, Port Louis, Mauritius.

(6) Consists of (a) 12,500 shares held of record by Dr. Watts and (b) 2,802,638 shares of restricted stock held of record by the Watts Family 2015 Trust dated July 7, 2015, for which Dr. Watts serves as trustee and which vest on February 23, 2019.

(7) Consists of (a) 685,089 shares of restricted stock held of record by the Schuth Family Trust, for which Dr. Schuth serves as trustee, which vest on March 17, 2019 and (b) 125,000 shares subject to options exercisable within 60 days of November 24, 2017, none of which have vested as of such date.

(8) Consists of 1,000,000 shares held of record by The Steve Edward Krognes Revocable Trust, for which Mr. Krognes serves as a trustee, of which 239,584 shares are subject to repurchase by us at the original purchase price as of November 24, 2017.

(9) Consists of (a) 46,875 shares held of record by Dr. Ho, all of which are subject to repurchase by us at the original purchase price as of November 24, 2017, (b) 235,890 shares held of record by the Rohatgi-Ho Family 2009 Revocable Trust, for which Dr. Ho serves as trustee, of which 89,063 shares are subject to repurchase by us at the original purchase price as of November 24, 2017, (c) 25,000 shares held of record by The Rohatgi-Ho Irrevocable GST Trust, for which Dr. Ho serves as trustee, of which 9,896 shares are subject to repurchase by us at the original purchase price as of November 24, 2017 and (d) 176,610 shares subject to options exercisable within 60 days of November 24, 2017, of which 46,875 have vested as of such date.

(10) Consists of (a) 62,500 shares held of record by Dr. Sato, (b) 75,000 shares of restricted stock held of record by Dr. Sato, which vest on April 17, 2019 and (c) 12,500 shares subject to options exercisable within 60 days of November 24, 2017, all of which have vested as of such date.

(11) Dr. Cole, a member of our board of directors, is a member of Flagship V GP but does not have voting or investment control with respect to the shares held by Flagship V. Dr. Cole disclaims beneficial ownership of all shares held by Flagship V.

(12) Consists of (a) 75,000 shares of restricted stock held of record by Mr. Flatley, which vest on April 17, 2019 and (b) 250,000 shares held of record by The Flatley Family Trust, for which Mr. Flatley serves as a trustee.

(13) Consists of the shares described in footnote (2) above. Mr. Nelsen is a managing director of AVP VIII LLC and shares voting and investment control with respect to these shares. Mr. Nelsen disclaims beneficial ownership of all shares held by ARCH Venture Fund VIII except to the extent of any pecuniary interest therein.

(14) Consists of (a) 75,000 shares of restricted stock held of record by Dr. Schenkein, which vest on April 17, 2019, (b) 105,225 shares held of record by the David P. Schenkein 2015 Denali Qualified Annuity Trust, for which Dr. Schenkein serves as a trustee, (c) 19,774 shares held of record by the David P. Schenkein 2004 Revocable Trust, for which Dr. Schenkein serves as a trustee, (d) 105,225 shares held of record by the Amy P. Schenkein 2015 Denali Qualified Annuity Trust, for which Dr. Schenkein serves as a trustee and (e) 19,774 shares held of record by the Amy P. Schenkein 2004 Revocable Trust, for which Dr. Schenkein serves as a trustee.

(15) Consists of (a) 25,000 shares held of record by Dr. Tessier-Lavigne and (b) 3,114,043 shares of restricted stock held of record by Dr. Tessier-Lavigne, which vest on March 24, 2019.
(16) Consists of (a) 20,117,392 shares beneficially owned by our current executive officers and directors, of which 385,418 shares may be repurchased by us at the original purchase price as of such date, and (b) 314,110 shares subject to options exercisable within 60 days of November 24, 2017, of which 59,375 have vested as of such date.

DESCRIPTION OF CAPITAL STOCK

The following descriptions of our capital stock and certain provisions of our amended and restated certificate of incorporation and amended and restated bylaws are summaries and are qualified by reference to the amended and restated certificate of incorporation and the amended and restated bylaws that will be in effect upon completion of this offering. Copies of these documents will be filed with the SEC as exhibits to our registration statement, of which this prospectus forms a part. The descriptions of the common stock and preferred stock reflect changes to our capital structure that will occur upon the completion of this offering.

Upon the completion of this offering and the filing of our amended and restated certificate of incorporation to be effective upon completion of this offering, our authorized capital stock will consist of 440,000,000 shares of capital stock, par value $0.01 per share, of which:

- 400,000,000 shares are designated as common stock; and
- 40,000,000 shares are designated as preferred stock.

Assuming the conversion of all outstanding shares of our convertible preferred stock issued as of September 30, 2017 into shares of our common stock (including 1,764,705 shares of our Series B-2 convertible preferred stock issued after September 30, 2017), which will occur upon the completion of this offering, as of September 30, 2017 there are 74,090,587 shares of our common stock outstanding held by 148 stockholders of record, and no shares of our preferred stock outstanding. Our board of directors is authorized, without stockholder approval except as required by the listing standard of NASDAQ, to issue additional shares of our capital stock.

Common Stock

Voting Rights

Each holder of common stock is entitled to one vote for each share on all matters submitted to a vote of the stockholders, including the election of directors. Our certificate of incorporation and bylaws to be in effect upon the completion of this offering do not provide for cumulative voting rights. Because of this, the holders of a plurality of the shares of common stock entitled to vote in any election of directors can elect all of the directors standing for election, if they should so choose. With respect to matters other than the election of directors, at any meeting of the stockholders at which a quorum is present or represented, the affirmative vote of a majority of the voting power of the shares present in person or represented by proxy at such meeting and entitled to vote on the subject matter shall be the act of the stockholders, except as otherwise required by law. The holders of a majority of the stock issued and outstanding and entitled to vote, present in person or represented by proxy, shall constitute a quorum for the transaction of business at all meetings of the stockholders.

Dividends

Subject to preferences that may be applicable to any then-outstanding preferred stock, holders of our common stock are entitled to receive dividends, if any, as may be declared from time to time by our board of directors out of legally available funds.

Liquidation

In the event of our liquidation, dissolution or winding up, holders of our common stock will be entitled to share ratably in the net assets legally available for distribution to stockholders after the payment of all of our debts and other liabilities and the satisfaction of any liquidation preference granted to the holders of any then-outstanding shares of preferred stock.

Rights and Preferences

Holders of our common stock have no preemptive, conversion, subscription or other rights, and there are no redemption or sinking fund provisions applicable to our common stock. The rights, preferences and privileges of the holders of our common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of our preferred stock that we may designate in the future.

Fully Paid and Nonassessable

All of our outstanding shares of common stock are, and the shares of common stock to be issued in this offering, upon payment and delivery in accordance with the underwriting agreement, will be fully paid and nonassessable.

Preferred Stock

Upon the closing of this offering, our board of directors will have the authority, without further action by the stockholders, to issue up to 40,000,000 shares of preferred stock in one or more series and to fix the rights, preferences, privileges and restrictions thereof. These rights, preferences and privileges could include dividend rights, conversion rights, voting rights, redemption rights, liquidation preferences, sinking fund terms and the number of shares constituting any series or the designation of such series, any or all of which may be greater than the rights of common stock. The issuance of preferred stock could adversely affect the voting power of holders of common stock and the likelihood that such holders will receive dividend payments and payments upon liquidation. In addition, the issuance of preferred stock could have the effect of delaying, deferring or preventing change in our control or other corporate action. Upon closing of this offering, no shares of preferred stock will be outstanding, and we have no present plan to issue any shares of preferred stock.

Options

As of September 30, 2017, we had outstanding options to purchase an aggregate of 6,179,687 shares of our common stock, with a weighted-average exercise price of approximately $3.06 per share, under our 2015 Plan. After September 30, 2017, we issued options to purchase an aggregate of 194,000 shares of our common stock, with a weighted-average exercise price of $11.64 per share, under our 2015 Plan.

Registration Rights

After the completion of this offering, under our investors' rights agreement, as amended, the holders of approximately 64,913,502 shares of common stock or their transferees, have the right to require us to register the offer and sale of their shares, or to include their shares in any registration statement we file, in each case as described below.

Demand Registration Rights

After the completion of this offering, the holders of up to 64,913,502 shares of our common stock will be entitled to certain demand registration rights. At any time beginning 180 days after the effective date of this offering, holders of at least a majority of the shares having registration rights then outstanding can request that we file a registration statement to register the offer and sale of their shares. We are obligated to effect only two such registrations. Each such request for registration must cover securities the anticipated aggregate public offering price of which, before payment of underwriting discounts and commissions, is at least $10 million. These demand registration rights are

subject to specified conditions and limitations, including the right of the underwriters to limit the number of shares included in any such registration under certain circumstances. If we determine that it would be seriously detrimental to us and our stockholders to effect such a demand registration, we have the right to defer such registration, not more than twice in any 12-month period, for a period of up to 60 days.

Form S-3 Registration Rights

After the completion of this offering, the holders of up to 64,913,502 shares of our common stock will be entitled to certain Form S-3 registration rights. At any time we are eligible to file a registration statement on Form S-3, at least twenty percent of the shares having these rights then outstanding can request that we register the offer and sale of their shares of our common stock on a registration statement on Form S-3 so long as the request covers securities the anticipated aggregate public offering price of which, before payment of underwriting discounts and commissions, is at least $5 million. These stockholders may make an unlimited number of requests for registration on a registration statement on Form S-3. However, we will not be required to effect a registration on Form S-3 if we have effected two such registrations within the 12-month period preceding the date of the request. Additionally, if we determine that it would be seriously detrimental to us and our stockholders to effect such a demand registration, we have the right to defer such registration, not more than twice in any 12-month period, for a period of up to 60 days.

Piggyback Registration Rights

After the completion of this offering, the holders of up to 64,913,502 shares of our common stock will be entitled to certain “piggyback” registration rights. If we propose to register the offer and sale of shares of our common stock under the Securities Act, all holders of these shares then outstanding can request that we include their shares in such registration, subject to certain marketing and other limitations, including the right of the underwriters to limit the number of shares included in any such registration statement under certain circumstances. As a result, whenever we propose to file a registration statement under the Securities Act, other than with respect to (1) a registration related to any employee benefit plan or a corporate reorganization or other transaction covered by Rule 145 promulgated under the Securities Act, (2) a registration in which the only stock being registered is common stock issuable upon conversion of debt securities also being registered or (3) a registration on any form that does not include substantially the same information as would be required to be included in a registration statement covering the sale of our common stock, the holders of these shares are entitled to notice of the registration and have the right, subject to certain limitations, to include their shares in the registration.

Expenses of Registration

We will pay all expenses relating to any demand registrations, Form S-3 registrations and piggyback registrations, subject to specified exceptions.

Termination

The registration rights terminate upon the earliest of (1) the date that is five years after the closing of this offering, (2) as to a given holder of registration rights, when such holder of registration rights can sell all of such holder’s registrable securities in a three-month period pursuant to Rule 144 promulgated under the Securities Act and (3) the closing of a deemed liquidation event.

Anti-Takeover Effects of Certain Provisions of Delaware Law, Our Amended and Restated Certificate of Incorporation and Our Amended and Restated Bylaws

Certain provisions of Delaware law and certain provisions that will be included in our amended and restated certificate of incorporation and amended and restated bylaws summarized below may be deemed to have an anti-takeover effect and may delay, deter, or prevent a tender offer or takeover attempt that a stockholder might consider to be in its best interests, including attempts that might result in a premium being paid over the market price for the shares held by stockholders.

Preferred Stock

Our amended and restated certificate of incorporation will contain provisions that permit our board of directors to issue, without any further vote or action by the stockholders, shares of preferred stock in one or more series and, with respect to each such series, to fix the number of shares constituting the series and the designation of the series, the voting rights (if any) of the shares of the series, and the powers, preferences or relative, participation, optional and other special rights, if any, and any qualifications, limitations or restrictions, of the shares of such series.

Classified Board of Directors

Our amended and restated certificate of incorporation will provide that our board of directors is divided into three classes, designated Class I, Class II, and Class III. Each class will be an equal number of directors, as nearly as possible, consisting of one-third of the total number of directors constituting our entire board of directors. The term of initial Class I directors shall terminate on the date of the 2018 annual meeting, the term of the initial Class II directors shall terminate on the date of the 2019 annual meeting, and the term of the initial Class III directors shall terminate on the date of the 2020 annual meeting. At each annual meeting of stockholders beginning in 2018, successors to the class of directors whose term expires at that annual meeting will be elected for a three-year term.

Removal of Directors

Our amended and restated certificate of incorporation will provide that stockholders may only remove a director for cause by a vote of no less than a majority of the shares present in person or by proxy at the meeting and entitled to vote.

Director Vacancies

Our amended and restated certificate of incorporation will authorize only our board of directors to fill vacant directorships.

No Cumulative Voting

Our amended and restated certificate of incorporation will provide that stockholders do not have the right to cumulate votes in the election of directors.

Special Meetings of Stockholders

Our amended and restated certificate of incorporation and amended and restated bylaws will provide that, except as otherwise required by law, special meetings of the stockholders may be called only by an officer at the request of a majority of our board of directors, by the chairperson of our board of directors, or by our Chief Executive Officer.

Advance Notice Procedures for Director Nominations

Our bylaws will provide that stockholders seeking to nominate candidates for election as directors at an annual or special meeting of stockholders must provide timely notice thereof in writing. To be timely, a stockholder's notice generally will have to be delivered to and received at our principal executive offices before notice of the meeting is issued by the secretary of the company, with such notice being served not less than 90 nor more than 120 days before the meeting. Although the amended and restated bylaws will not give our board of directors the power to approve or disapprove stockholder nominations of candidates to be elected at an annual meeting, the amended and restated bylaws may have the effect of precluding the conduct of certain business at a meeting if the proper procedures are not followed or may discourage or deter a potential acquirer from conducting a solicitation of proxies to elect its own slate of directors or otherwise attempting to obtain control of the company.

Action by Written Consent

Our amended and restated certificate of incorporation and amended and restated bylaws will provide that any action to be taken by the stockholders must be effected at a duly called annual or special meeting of stockholders and may not be effected by written consent.

Amending our Certificate of Incorporation and Bylaws

Our amended and restated certificate of incorporation may be amended or altered in any manner provided by the DGCL. Our amended and restated bylaws may be adopted, amended, altered, or repealed by stockholders only upon approval of at least majority of the voting power of all the then outstanding shares of the common stock, except for any amendment of the above provisions, which would require the approval of a two-thirds majority of our then outstanding common stock. Additionally, our amended and restated certificate of incorporation will provide that our bylaws may be amended, altered, or repealed by our board of directors.

Authorized but Unissued Shares

Our authorized but unissued shares of common stock and preferred stock will be available for future issuances without stockholder approval, except as required by the listing standards of NASDAQ, and could be utilized for a variety of corporate purposes, including future offerings to raise additional capital, acquisitions and employee benefit plans. The existence of authorized but unissued and unreserved common stock and preferred stock could render more difficult or discourage an attempt to obtain control of the company by means of a proxy contest, tender offer, merger or otherwise.

Exclusive Jurisdiction

Our amended and restated bylaws will provide that, unless we consent to the selection of an alternative forum, the Court of Chancery of the State of Delaware shall be the sole and 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 arising pursuant to the DGCL, any action regarding our amended and restated certificate of incorporation or our amended and restated bylaws or 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.

Business Combinations with Interested Stockholders

Subject to certain exceptions, Section 203 of the DGCL prohibits a public Delaware corporation from engaging in a business combination (as defined in such section) with an "interested stockholder"

(defined generally as any person who beneficially owns 15% or more of the outstanding voting stock of such corporation or any person affiliated with such person) for a period of three years following the time that such stockholder became an interested stockholder, unless (i) prior to such time the board of directors of such corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder; (ii) upon consummation of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of such corporation at the time the transaction commenced (excluding for purposes of determining the voting stock of such corporation outstanding (but not the outstanding voting stock owned by the interested stockholder) those shares owned (A) by persons who are directors and also officers of such corporation and (B) by employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer); or (iii) at or subsequent to such time the business combination is approved by the board of directors of such corporation and authorized at a meeting of stockholders (and not by written consent) by the affirmative vote of at least 66 2/3% of the outstanding voting stock of such corporation not owned by the interested stockholder.

Our amended and restated certificate of incorporation and our amended and restated bylaws will provide that we must indemnify our directors and officers to the fullest extent authorized by the DGCL. We are expressly authorized to carry, and we intend to carry, directors' and officers' insurance providing coverage for our directors, officers and certain employees for some liabilities. We believe that these indemnification provisions and insurance are useful to attract and retain qualified directors and executive directors.

The limitation on liability and indemnification provisions in our certificate of incorporation and bylaws may discourage stockholders from bringing a lawsuit against directors for breach of their fiduciary duty. These provisions may also have the effect of reducing the likelihood of derivative litigation against directors and officers, even though such an action, if successful, might otherwise benefit us and our stockholders. In addition, your investment may be adversely affected to the extent we pay the costs of settlement and damage awards against directors and officers pursuant to these indemnification provisions.

Listing

Our common stock has been approved for listing on the NASDAQ Global Select Market under the symbol "DNLI."

Transfer Agent and Registrar

Upon completion of this offering, the transfer agent and registrar for our common stock will be American Stock Transfer & Trust Company, LLC. The transfer agent and registrar's address is 6201 15th Avenue, Brooklyn, New York 11219.

SHARES ELIGIBLE FOR FUTURE SALE

Prior to this offering, there has been no public market for our common stock, and we cannot assure investors that there will be an active public market for our common stock following this offering. We cannot predict what effect, if any, sales of our shares in the public market or the availability of shares for sale will have on the market price of our common stock. Future sales of substantial amounts of common stock in the public market, including shares issued upon exercise of outstanding options, or the perception that such sales may occur, however, could adversely affect the market price of our common stock and also could adversely affect our future ability to raise capital through the sale of our common stock or other equity-related securities of ours at times and prices we believe appropriate.

Upon completion of this offering, based on our shares outstanding as of September 30, 2017 and after giving effect to the conversion of all outstanding shares of our convertible preferred stock (including 1,764,705 shares issuable upon conversion of our Series B-2 convertible preferred stock), 87,979,475 shares of our common stock will be outstanding, or 90,062,808 shares of common stock if the underwriters exercise their option to purchase additional shares in full. All of the shares of common stock expected to be sold in this offering will be freely tradable without restriction or further registration under the Securities Act unless held by our "affiliates," as that term is defined in Rule 144 under the Securities Act. The remaining outstanding shares of our common stock will be deemed "restricted securities" as that term is defined under Rule 144. Restricted securities may be sold in the public market only if their offer and sale is registered under the Securities Act or if the offer and sale of those securities qualify for an exemption from registration, including exemptions provided by Rules 144 and 701 under the Securities Act, which are summarized below.

As a result of the lock-up agreements and market stand-off provisions described below and the provisions of Rules 144 or 701 and no exercise of the underwriters' option to purchase additional shares, the shares of our common stock that will be deemed "restricted securities" will be available for sale in the public market following the completion of this offering as follows:

- 13,888,888 shares will be eligible for sale on the date of this prospectus; and
- 74,090,587 shares will be eligible for sale upon expiration of the lock-up agreements and market stand-off provisions described below, beginning more than 180 days after the date of this prospectus.

Lock-Up Agreements and Market Standoff Agreements

Our officers, directors and the holders of substantially all of our capital stock and options have entered into lock-up agreements with the underwriters or market standoff agreements with us under which they have agreed, subject to certain exceptions, not to dispose of or hedge any of their common stock or securities convertible into or exchangeable for shares of common stock during the period from the date of this prospectus continuing through the date 180 days after the date of this prospectus, except with the prior consent of Goldman Sachs & Co. LLC, Morgan Stanley & Co. LLC and J.P. Morgan Securities LLC. See the section titled "Underwriting" for additional information.

Rule 144

Rule 144, as currently in effect, generally provides that, once we have been subject to the public company reporting requirements of Section 13 or Section 15(d) of the Exchange Act for at least 90 days, a stockholder who is not deemed to have been one of our affiliates at any time during the preceding 90 days and who has beneficially owned the shares of our capital stock proposed to be sold for at least six months is entitled to sell such shares in reliance upon Rule 144 without complying with the volume limitation, manner of sale or notice conditions of Rule 144. If such stockholder has beneficially owned the shares of our capital stock proposed to be sold for at least one year, then such

person is entitled to sell such shares in reliance upon Rule 144 without complying with any of the conditions of Rule 144.

Rule 144 also provides that a stockholder who is deemed to have been one of our affiliates at any time during the preceding 90 days and who has beneficially owned the shares of our common stock proposed to be sold for at least six months is entitled to sell such shares in reliance upon Rule 144 within any three-month period beginning 90 days after the date of this prospectus a number of shares that does not exceed the greater of the following:

- 1% of the number of shares of our capital stock then outstanding, which will equal 879,795 shares immediately after the completion of this offering; or
- the average weekly trading volume of our common stock during the four calendar weeks preceding the filing of a notice on Form 144 with respect to such sale.

Sales of our capital stock made in reliance upon Rule 144 by a stockholder who is deemed to have been one of our affiliates at any time during the preceding 90 days are also subject to the current public information, manner of sale, and notice conditions of Rule 144.

Rule 701

Rule 701 generally provides that, once we have been subject to the public company reporting requirements of Section 13 or Section 15(d) of the Exchange Act for at least 90 days, a stockholder who purchased shares of our common stock pursuant to a written compensatory benefit plan or contract and who is not deemed to have been one of our affiliates at any time during the preceding 90 days may sell such shares in reliance upon Rule 144 without complying with the current public information or holding period conditions of Rule 144. Rule 701 also provides that a stockholder who purchased shares of our common stock pursuant to a written compensatory benefit plan or contract and who is deemed to have been one of our affiliates during the preceding 90 days may sell such shares under Rule 144 without complying with the holding period condition of Rule 144. However, all stockholders who purchased shares of our common stock pursuant to a written compensatory benefit plan or contract are required to wait until 90 days after the date of this prospectus before selling such shares pursuant to Rule 701.

Registration Rights

After the completion of this offering, the holders of up to 64,913,502 shares of our common stock will be entitled to certain rights with respect to the registration of such shares under the Securities Act. The registration of these shares of our common stock under the Securities Act would result in these shares becoming eligible for sale in the public market without restriction under the Securities Act immediately upon the effectiveness of such registration, subject to the Rule 144 limitations applicable to affiliates. See the section titled “Description of Capital Stock—Registration Rights” for a description of these registration rights.

Registration Statement

In connection with this offering, we intend to file a registration statement on Form S-8 under the Securities Act to register all of the shares of our common stock subject to equity awards outstanding or reserved for issuance under our equity compensation plans. The shares of our common stock covered by such registration statement will be eligible for sale in the public market without restriction under the Securities Act immediately upon the effectiveness of such registration statement, subject to vesting restrictions, the conditions of Rule 144 applicable to affiliates and any applicable market standoff agreements and lock-up agreements. See the section titled “Executive Compensation—Employee Benefit and Stock Plans” for a description of our equity compensation plans.

MATERIAL U.S. FEDERAL INCOME AND ESTATE TAX CONSIDERATIONS FOR NON-U.S. HOLDERS OF OUR COMMON STOCK

The following is a summary of the material U.S. federal income tax consequences of the ownership and disposition of our common stock acquired in this offering by a "non-U.S. holder" (as defined below), but does not purport to be a complete analysis of all the potential tax considerations relating thereto. This summary is based upon the provisions of the United States Internal Revenue Code of 1986, as amended, or the Code, Treasury Regulations promulgated thereunder, administrative rulings and judicial decisions, all as of the date hereof. These authorities may be changed, possibly retroactively, so as to result in U.S. federal income tax consequences different from those set forth below. We have not sought, and do not intend to seek, any ruling from the Internal Revenue Service, or IRS, with respect to the statements made and the conclusions reached in the following summary, and there can be no assurance that the IRS or a court will agree with such statements and conclusions.

This summary also does not address the tax considerations arising under the laws of any non-U.S., state or local jurisdiction or under U.S. federal gift and estate tax rules, except to the limited extent set forth below. In addition, this discussion does not address tax considerations applicable to an investor's particular circumstances or to investors that may be subject to special tax rules, including, without limitation:

- banks, insurance companies, regulated investment companies, real estate investment trusts or other financial institutions;
- persons subject to the alternative minimum tax or the tax on net investment income;
- tax-exempt organizations;
- pension plans and tax-qualified retirement plans;
- controlled foreign corporations, passive foreign investment companies and corporations that accumulate earnings to avoid U.S. federal income tax;
- brokers or dealers in securities or currencies;
- traders in securities that elect to use a mark-to-market method of accounting for their securities holdings;
- persons that own, or are deemed to own, more than five percent of our capital stock (except to the extent specifically set forth below);
- certain former citizens or long-term residents of the United States;
- persons who hold our common stock as a position in a hedging transaction, "straddle," "conversion transaction" or other risk reduction transaction;
- persons who hold or receive our common stock pursuant to the exercise of any option or otherwise as compensation;
- persons who do not hold our common stock as a capital asset within the meaning of Section 1221 of the Code (generally, property held for investment); or
- persons deemed to sell our common stock under the constructive sale provisions of the Code.

In addition, if a partnership, entity or arrangement classified as a partnership or flow-through entity for U.S. federal income tax purposes holds our common stock, the tax treatment of a partner generally will depend on the status of the partner and upon the activities of the partnership or other entity. A partner in a partnership or other such entity that will hold our common stock should consult his, her or its own tax advisor regarding the tax consequences of the ownership and disposition of our common stock through a partnership or other such entity, as applicable.

You are urged to consult your tax advisor with respect to the application of the U.S. federal income tax laws to your particular situation, as well as any tax consequences of the purchase, ownership and disposition of our common stock arising under the U.S. federal gift or estate tax rules or under the laws of any state, local, non-U.S. or other taxing jurisdiction or under any applicable tax treaty.

Non-U.S. Holder Defined

For purposes of this discussion, you are a "non-U.S. holder" if you are a beneficial owner of our common stock that, for U.S. federal income tax purposes, is not a partnership or:

- an individual who is a citizen or resident of the United States;
- a corporation or other entity taxable as a corporation created or organized in the United States or under the laws of the United States or any political subdivision thereof, or otherwise treated as such for U.S. federal income tax purposes;
- an estate whose income is subject to U.S. federal income tax regardless of its source; or
- a trust (x) whose administration is subject to the primary supervision of a U.S. court and that has one or more U.S. persons who have the authority to control all substantial decisions of the trust or (y) that has made a valid election under applicable Treasury Regulations to be treated as a U.S. person.

Distributions

As described in the section titled "Dividend Policy," we have never declared or paid cash dividends on our common stock, and we do not anticipate paying any dividends on our common stock following the completion of this offering. However, if we do make distributions on our common stock, those payments will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. To the extent those distributions exceed both our current and our accumulated earnings and profits, the excess will constitute a return of capital and will first reduce your basis in our common stock, but not below zero, and then will be treated as gain from the sale of stock.

Subject to the discussions below on effectively connected income and Foreign Account Tax Compliance Act, or FATCA, withholding, any dividend paid to you generally will be subject to U.S. federal withholding tax either at a rate of 30% of the gross amount of the dividend or such lower rate as may be specified by an applicable income tax treaty between the United States and your country of residence. In order to receive a reduced treaty rate, you must provide the applicable withholding agent with an IRS Form W-8BEN or W-8BEN-E or other appropriate version of IRS Form W-8 certifying qualification for the reduced rate. A non-U.S. holder of shares of our common stock eligible for a reduced rate of U.S. federal withholding tax pursuant to an income tax treaty may obtain a refund of any excess amounts withheld by filing an appropriate claim for refund with the IRS. If the non-U.S. holder holds our common stock through a financial institution or other agent acting on the non-U.S. holder's behalf, the non-U.S. holder will be required to provide appropriate documentation to the agent, which then will be required to provide certification to the applicable withholding agent, either directly or through other intermediaries.

Dividends received by you that are treated as effectively connected with your conduct of a U.S. trade or business (and, if required by an applicable income tax treaty, such dividends are attributable to a permanent establishment or fixed base maintained by you in the United States) are generally exempt from the 30% U.S. federal withholding tax, subject to the discussion below on backup withholding and FATCA withholding. In order to obtain this exemption, you must provide the applicable withholding

agent with a properly executed IRS Form W-8ECI or other applicable IRS Form W-8 properly certifying such exemption. Such effectively connected dividends, although not subject to U.S. federal withholding tax, are taxed at the same graduated rates applicable to U.S. persons, net of certain deductions and credits, subject to an applicable income tax treaty providing otherwise. In addition, if you are a corporate non-U.S. holder, dividends you receive that are effectively connected with your conduct of a U.S. trade or business may also be subject to a branch profits tax at a rate of 30% or such lower rate as may be specified by an applicable income tax treaty between the United States and your country of residence. You should consult your tax advisor regarding the tax consequences of the ownership and disposition of our common stock, including any applicable tax treaties that may provide for different rules.

Gain on Disposition of Common Stock

Subject to the discussion below regarding backup withholding and FATCA withholding, you generally will not be required to pay U.S. federal income tax on any gain realized upon the sale or other disposition of our common stock unless:

- the gain is effectively connected with your conduct of a U.S. trade or business (and, if an applicable income tax treaty so provides, the gain is attributable to a permanent establishment or fixed base maintained by you in the United States);
- you are an individual who is present in the United States for a period or periods aggregating 183 days or more during the calendar year in which the sale or disposition occurs and certain other conditions are met; or
- our common stock constitutes a United States real property interest by reason of our status as a “United States real property holding corporation,” or USRPHC, for U.S. federal income tax purposes at any time within the shorter of the five-year period preceding your disposition of, or your holding period for, our common stock.

We believe that we are not currently and will not become a USRPHC for U.S. federal income tax purposes, and the remainder of this discussion so assumes. However, because the determination of whether we are a USRPHC depends on the fair market value of our U.S. real property interests relative to the fair market value of our U.S. and worldwide real property interests plus our other business assets, there can be no assurance that we will not become a USRPHC in the future. Even if we become a USRPHC, however, as long as our common stock is regularly traded on an established securities market, your common stock will be treated as U.S. real property interests only if you actually (directly or indirectly) or constructively hold more than five percent of such regularly traded common stock at any time during the shorter of the five-year period preceding your disposition of, or your holding period for, our common stock.

If you are a non-U.S. holder described in the first bullet above, you will be required to pay tax on the gain derived from the sale (net of certain deductions and credits) under regular graduated U.S. federal income tax rates, and a corporate non-U.S. holder described in the first bullet above also may be subject to the branch profits tax at a 30% rate, or such lower rate as may be specified by an applicable income tax treaty. If you are an individual non-U.S. holder described in the second bullet above, you will be subject to tax at 30% (or such lower rate specified by an applicable income tax treaty) on the gain derived from the sale, which gain may be offset by U.S. source capital losses for the year, provided you have timely filed U.S. federal income tax returns with respect to such losses. You should consult your tax advisor regarding any applicable income tax or other treaties that may provide for different rules.

Federal Estate Tax

Our common stock beneficially owned by an individual who is not a citizen or resident of the United States (as defined for U.S. federal estate tax purposes) at the time of his or her death will generally be includable in the decedent's gross estate for U.S. federal estate tax purposes. Such stock, therefore, may be subject to U.S. federal estate tax, unless an applicable estate tax treaty provides otherwise.

Backup Withholding and Information Reporting

Generally, we must report annually to the IRS the amount of dividends paid to you, your name and address, and the amount of tax withheld, if any. A similar report will be sent to you. Pursuant to applicable income tax treaties or other agreements, the IRS may make these reports available to tax authorities in your country of residence.

Payments of dividends on or of proceeds from the disposition of our common stock made to you may be subject to information reporting and backup withholding at a current rate of 28% unless you establish an exemption, for example, by properly certifying your non-U.S. status on a properly completed IRS Form W-8BEN or W-8BEN-E or another appropriate version of IRS Form W-8. Notwithstanding the foregoing, backup withholding and information reporting may apply if the applicable withholding agent has actual knowledge, or reason to know, that you are a U.S. person.

Backup withholding is not an additional tax; rather, the U.S. federal income tax liability of persons subject to backup withholding will be reduced by the amount of tax withheld. If withholding results in an overpayment of taxes, a refund or credit may generally be obtained from the IRS, provided that the required information is furnished to the IRS in a timely manner.

Foreign Account Tax Compliance Act (FATCA)

Provisions of the Code commonly referred to as FATCA, Treasury Regulations issued thereunder and official IRS guidance generally impose a U.S. federal withholding tax of 30% on dividends on, and the gross proceeds from a sale or other disposition of our common stock, paid to a "foreign financial institution" (as specially defined under these rules), unless such institution enters into an agreement with the U.S. government to, among other things, withhold on certain payments and to collect and provide to the U.S. tax authorities substantial information regarding the U.S. account holders of such institution (which includes certain equity and debt holders of such institution, as well as certain account holders that are foreign entities with U.S. owners) or otherwise establishes an exemption. FATCA also generally imposes a U.S. federal withholding tax of 30% on dividends on, and the gross proceeds from, a sale or other disposition of our common stock paid to a "non-financial foreign entity" (as specially defined under these rules), unless such entity provides the withholding agent with a certification identifying the substantial direct and indirect U.S. owners of the entity, certifies that it does not have any substantial U.S. owners, or otherwise establishes an exemption.

The withholding obligations under FATCA generally apply to dividends on our common stock and under current transition rules are expected to apply to the payment of gross proceeds of a sale or other disposition of our common stock made on or after January 1, 2019. The withholding tax will apply regardless of whether the payment otherwise would be exempt from U.S. nonresident and backup withholding tax, including under the other exemptions described above. Under certain circumstances, a non-U.S. holder might be eligible for refunds or credits of such taxes. An intergovernmental agreement between the United States and an applicable foreign country may modify the requirements described in this section. Prospective investors are encouraged to consult with their own tax advisors regarding the application of FATCA withholding to their investment in, and ownership and disposition of, our common stock.

The preceding discussion of U.S. federal tax considerations is for general information only. It is not tax advice to investors in their particular circumstances. Each prospective investor should consult its own tax advisor regarding the particular U.S. federal, state and local and non-U.S. tax consequences of purchasing, holding and disposing of our common stock, including the consequences of any proposed change in applicable laws.

UNDERWRITING

We and the underwriters named below have entered into an underwriting agreement with respect to the shares being offered. Subject to certain conditions, each underwriter has severally agreed to purchase the number of shares indicated in the following table. Goldman Sachs & Co. LLC, Morgan Stanley & Co. LLC and J.P. Morgan Securities LLC are the representatives of the underwriters.

Underwriters	Number of Shares
Goldman Sachs & Co. LLC	4,166,667
Morgan Stanley & Co. LLC	3,819,444
J.P. Morgan Securities LLC	3,819,444
Evercore Group L.L.C.	2,083,333
Total	13,888,888

The underwriters are committed to take and pay for all of the shares being offered, if any are taken, other than the shares covered by the option described below unless and until this option is exercised.

Certain of our existing stockholders, including one that beneficially owns more than 5% of our outstanding common stock, have agreed to purchase approximately 5,300,000 shares of our common stock in this offering at the initial public offering price. The underwriters will receive the same underwriting discounts and commissions on the shares purchased by these stockholders as they will on the other shares sold to the public in this offering.

The underwriters have an option to buy up to an additional 2,083,333 shares from us to cover sales by the underwriters of a greater number of shares than the total number set forth in the table above. They may exercise that option for 30 days. If any shares are purchased pursuant to this option, the underwriters will severally purchase shares in approximately the same proportion as set forth in the table above.

The following table shows the per share and total underwriting discounts and commissions to be paid to the underwriters by us. Such amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase 2,083,333 additional shares.

Paid by the Company	No Exercise	Full Exercise
Per Share	$ 1.26	$ 1.26
Total	$ 17,499,999	$ 20,124,998

Shares sold by the underwriters to the public will initially be offered at the initial public offering price set forth on the cover of this prospectus. Any shares sold by the underwriters to securities dealers may be sold at a discount of up to $0.756 per share from the initial public offering price. After the initial offering of the shares, the representatives may change the offering price and the other selling terms. The offering of the shares by the underwriters is subject to receipt and acceptance and subject to the underwriters' right to reject any order in whole or in part.

We, our officers, directors, and holders of substantially all of our common stock and securities convertible into or exchangeable for our common stock have agreed that, without the prior written consent of the representatives on behalf of the underwriters, we and they will not, subject to certain exceptions, dispose of or hedge any common stock or securities convertible into or exchangeable for shares of common stock during the period from the date of this prospectus continuing through the date 180 days after the date of this prospectus. This agreement does not apply to any existing employee benefit plans. See the section titled "Shares Eligible for Future Sale" for a discussion of certain transfer restrictions.

Prior to the offering, there has been no public market for the shares. The initial public offering price was negotiated among the representatives and us. Among the factors considered in determining the initial public offering price of the shares, in addition to prevailing market conditions, were our historical performance, estimates of our business potential and earnings prospects, an assessment of our management and the consideration of the above factors in relation to market valuation of companies in related businesses.

Our common stock has been approved for listing on NASDAQ under the symbol “DNLI.”

In connection with the offering, the underwriters may purchase and sell shares of common stock in the open market. These transactions may include short sales, stabilizing transactions and purchases to cover positions created by short sales. Short sales involve the sale by the underwriters of a greater number of shares than they are required to purchase in the offering, and a short position represents the amount of such sales that have not been covered by subsequent purchases. A “covered short position” is a short position that is not greater than the amount of additional shares for which the underwriters’ option described above may be exercised. The underwriters may cover any covered short position by either exercising their option to purchase additional shares or purchasing shares in the open market. In determining the source of shares to cover the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase additional shares pursuant to the option described above. “Naked” short sales are any short sales that create a short position greater than the amount of additional shares for which the option described above may be exercised. The underwriters must cover any such naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in the offering. Stabilizing transactions consist of various bids for or purchases of common stock made by the underwriters in the open market prior to the completion of the offering.

The underwriters may also impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it, because the representatives have repurchased shares sold by or for the account of such underwriter in stabilizing or short covering transactions.

Purchases to cover a short position and stabilizing transactions, as well as other purchases by the underwriters for their own accounts, may have the effect of preventing or retarding a decline in the market price of our stock, and together with the imposition of the penalty bid, may stabilize, maintain or otherwise affect the market price of the common stock. As a result, the price of the common stock may be higher than the price that otherwise might exist in the open market. The underwriters are not required to engage in these activities and may end any of these activities at any time. These transactions may be effected on NASDAQ, in the over-the-counter market or otherwise.

European Economic Area

In relation to each Member State of the European Economic Area which has implemented the Prospectus Directive (each, a Relevant Member State), an offer to the public of our common stock may not be made in that Relevant Member State, except that an offer to the public in that Relevant Member State of our common stock may be made at any time under the following exemptions under the Prospectus Directive:

(a) to any legal entity which is a qualified investor as defined in the Prospectus Directive;

(b) to fewer than 150 natural or legal persons (other than qualified investors as defined in the Prospectus Directive), subject to obtaining the prior consent of the representatives for any such offer; or

(c) in any other circumstances falling within Article 3(2) of the Prospectus Directive;

provided that no such offer of shares of our common stock shall result in a requirement for the publication by us or any underwriter of a prospectus pursuant to Article 3 of the Prospectus Directive.

For the purposes of this provision, the expression an "offer to the public" in relation to our common stock in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and our common stock to be offered so as to enable an investor to decide to purchase our common stock, as the same may be varied in that Member State by any measure implementing the Prospectus Directive in that Member State, the expression "Prospectus Directive" means Directive 2003/71/EC (as amended), including by Directive 2010/73/EU and includes any relevant implementing measure in the Relevant Member State.

This European Economic Area selling restriction is in addition to any other selling restrictions set out below.

United Kingdom

In the United Kingdom, this prospectus is only addressed to and directed as qualified investors who are (i) investment professionals falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005 (the Order); or (ii) high net worth entities and other persons to whom it may lawfully be communicated, falling within Article 49(2)(a) to (d) of the Order (all such persons together being referred to as "relevant persons"). Any investment or investment activity to which this prospectus relates is available only to relevant persons and will only be engaged with relevant persons. Any person who is not a relevant person should not act or relay on this prospectus or any of its contents.

Canada

The common stock may be sold in Canada only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of the Securities Act (Ontario), and are permitted clients, as defined in National Instrument 31-103 Registration Requirements, Exemptions, and Ongoing Registrant Obligations. Any resale of the common stock must be made in accordance with an exemption form, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory of these rights or consult with a legal advisor.

Pursuant to section 3A.3 of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

Hong Kong

The common stock may not be offered or sold in Hong Kong by means of any document other than (i) in circumstances which do not constitute an offer to the public within the meaning of the Companies (Winding Up and Miscellaneous Provisions) Ordinance (Cap. 32 of the Laws of Hong Kong), or Companies (Winding Up and Miscellaneous Provisions) Ordinance, or which do not constitute an invitation to the public within the meaning of the Securities and Futures Ordinance (Cap. 571 of the Laws of Hong Kong), or Securities and Futures Ordinance, or (ii) to "professional investors" as defined in the Securities and Futures Ordinance and any rules made thereunder, or (iii) in other circumstances which do not result in the document being a "prospectus" as defined in the Companies (Winding Up and Miscellaneous Provisions) Ordinance, and no advertisement, invitation or document relating to the shares may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong (except if permitted to do so under the securities laws of Hong Kong) other than with respect to shares of common stock which are or are intended to be disposed of only to persons outside Hong Kong or only to "professional investors" in Hong Kong as defined in the Securities and Futures Ordinance and any rules made thereunder.

Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the common stock may not be circulated or distributed, nor may the common stock be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor (as defined under Section 4A of the Securities and Futures Act, Chapter 289 of Singapore, or the SFA, under Section 274 of the SFA, (ii) to a relevant person (as defined in Section 275(2) of the SFA) pursuant to Section 275(1) of the SFA, or any person pursuant to Section 275(1A) of the SFA, and in accordance with the conditions specified in Section 275 of the SFA or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA, in each case subject to conditions set forth in the SFA.

Where the shares of common stock are subscribed or purchased under Section 275 of the SFA by a relevant person which is a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor, the securities (as defined in Section 239(1) of the SFA) of that corporation shall not be transferable for 6 months after that corporation has acquired the common stock under Section 275 of the SFA except: (1) to an institutional investor under Section 274 of the SFA or to a relevant person (as defined in Section 275(2) of the SFA), (2) where such transfer arises from an offer in that corporation's securities pursuant to Section 275(1A) of the SFA, (3) where no consideration is or will be given for the transfer, (4) where the transfer is by operation of law, (5) as specified in Section 276(7) of the SFA, or (6) as specified in Regulation 32 of the Securities and Futures (Offers of Investments) (Shares and Debentures) Regulations 2005 of Singapore, or Regulation 32.

Where the shares of common stock are subscribed or purchased under Section 275 of the SFA by a relevant person which is a trust (where the trustee is not an accredited investor (as defined in Section 4A of the SFA)) whose sole purpose is to hold investments and each beneficiary of the trust is an accredited investor, the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferable for 6 months after that trust has acquired the common stock under Section 275 of the SFA except: (1) to an institutional investor under Section 274 of the SFA or to a relevant person (as defined in Section 275(2) of the SFA), (2) where such transfer arises from an offer that is made on

terms that such rights or interest are acquired at a consideration of not less than S$200,000 (or its equivalent in a foreign currency) for each transaction (whether such amount is to be paid for in cash or by exchange of securities or other assets), (3) where no consideration is or will be given for the transfer, (4) where the transfer is by operation of law, (5) as specified in Section 276(7) of the SFA, or (6) as specified in Regulation 32.

Japan

The common stock has not been and will not be registered under the Financial Instruments and Exchange Act of Japan (Act No. 25 of 1948, as amended), or the FIEA. The common stock may not be offered or sold, directly or indirectly, in Japan or to or for the benefit of any resident of Japan (including any person resident in Japan or any corporation or other entity organized under the laws of Japan) or to others for reoffering or resale, directly or indirectly, in Japan or to or for the benefit of any resident of Japan, except pursuant to an exemption from the registration requirements of the FIEA and otherwise in compliance with any relevant laws and regulations of Japan.

We estimate that our share of the total expenses of the offering, excluding underwriting discounts and commissions, will be approximately $3,500,000. We have agreed to reimburse the underwriters for expenses related to any applicable state securities filings and to the Financial Industry Regulatory Authority incurred by them in connection with this offering in an amount up to $35,000. The underwriters have agreed to reimburse us, or will pay and not seek reimbursement from us, for certain out-of-pocket expenses incurred by us in connection with this offering.

We have agreed to indemnify the several underwriters against certain liabilities, including liabilities under the Securities Act.

The underwriters and their respective affiliates are full service financial institutions engaged in various activities, which may include sales and trading, commercial and investment banking, advisory, investment management, investment research, principal investment, hedging, market making, brokerage and other financial and non-financial activities and services. Certain of the underwriters and their respective affiliates have provided, and may in the future provide, a variety of these services to the issuer and to persons and entities with relationships with the issuer, for which they received or will receive customary fees and expenses.

In the ordinary course of their various business activities, the underwriters and their respective affiliates, officers, directors and employees may purchase, sell or hold a broad array of investments and actively trade securities, derivatives, loans, commodities, currencies, credit default swaps and other financial instruments for their own account and for the accounts of their customers, and such investment and trading activities may involve or relate to assets, securities and/or instruments of the issuer (directly, as collateral securing other obligations or otherwise) and/or persons and entities with relationships with the issuer. The underwriters and their respective affiliates may also communicate independent investment recommendations, market color or trading ideas and/or publish or express independent research views in respect of such assets, securities or instruments and may at any time hold, or recommend to clients that they should acquire, long and/or short positions in such assets, securities and instruments.

LEGAL MATTERS

The validity of the issuance of our common stock offered in this prospectus will be passed upon for us by Wilson Sonsini Goodrich & Rosati, Professional Corporation, Palo Alto, California. Davis Polk & Wardwell LLP, Menlo Park, California, is acting as counsel for the underwriters.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements at December 31, 2016 and 2015, and for each of the two years in the period ended December 31, 2016, as set forth in their report. We have included our consolidated financial statements in the prospectus and elsewhere in the registration statement in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND ADDITIONAL INFORMATION

We have filed with the SEC a registration statement on Form S-1 under the Securities Act with respect to the shares of our common stock offered by this prospectus. This prospectus, which constitutes a part of the registration statement, does not contain all of the information set forth in the registration statement, as permitted by the rules and regulations of the SEC. For further information with respect to us and our common stock, we refer you to the registration statement, including the exhibits filed as a part of the registration statement. Statements contained in this prospectus concerning the contents of any contract or any other document is not necessarily complete. If a contract or document has been filed as an exhibit to the registration statement, please see the copy of the contract or document that has been filed. Each statement in this prospectus relating to a contract or document filed as an exhibit is qualified in all respects by the filed exhibit. You may obtain copies of this information by mail from the Public Reference Section of the SEC, 100 F Street, N.E., Room 1580, Washington, D.C. 20549, at prescribed rates or view them online. You may obtain information on the operation of the public reference rooms by calling the SEC at 1-800-SEC-0330. The SEC also maintains an Internet website that contains the registration statement of which this prospectus forms a part, as well as the exhibits thereto. These documents, along with future reports, proxy statements and other information about us, are available at the SEC's website, www.sec.gov.

As a result of this offering, we will become subject to the information and reporting requirements of the Exchange Act, as amended, and, in accordance with this law, will file periodic reports, proxy statements and other information with the SEC. These periodic reports, proxy statements and other information will be available for inspection and copying at the SEC's public reference facilities and the website of the SEC referred to above. We also maintain a website at www.denalitherapeutics.com. Upon the completion of this offering, you may access these materials free of charge as soon as reasonably practicable after they are electronically filed with, or furnished to, the SEC. Information contained on our website is not a part of this prospectus, and the inclusion of our website address in this prospectus is an inactive textual reference only.

GLOSSARY

Abeta	amyloid beta
ALS	amyotrophic lateral sclerosis
AMP	average manufacturer price
Amyloid	complex proteins deposited in tissues that form the primary component of plaques characteristic of Alzheimer's disease
Amyloid plaques	accumulations of amyloid
ANDA	abbreviated new drug application to the FDA
APP	amyloid precursor protein
Assay	procedure to assess the amount or activity of a target entity
aSyn	alpha-synuclein
ATV	antibody transport vehicle
BACE1	beta-secretase 1
BBB	blood-brain barrier
Biomarker	a biological molecule found in blood, other bodily fluids or tissues that is a sign of a normal or abnormal process or of a condition or disease
BLA	biologics license application to the FDA
cGCPs	current good clinical practices promulgated by the FDA
cGMPs	current good manufacturing practices promulgated by the FDA
CHMP	Committee for Medicinal Products for Human Use
Cmax	predicted maximum concentration
CMO	third-party contract manufacturer
CMS	Centers for Medicare & Medicaid Services
CRO	contract research organization
CSF	cerebrospinal fluid
CTA	clinical trial application to the EMA
DAT	dopamine transporter imaging
Degenogenes	genes, that when mutated, cause, or are major risk factors for, neurodegenerative diseases
DLB	dementia with Lewy bodies
DNA	deoxyribonucleic acid
EEA	European Economic Area
EMA	European Medicines Agency
ETV	enzyme transport vehicle
Fabs	targets bound by the variable domains of an antibody or other therapeutic modalities

Fcabs	constant Fc domains of an antibody with non-native antigen binding activity
FDA	U.S. Food and Drug Administration
GAGs	glycosaminoglycans
GBA	glucocerebrosidase, a lysosomal enzyme
GCP	good clinical practice promulgated by the FDA
Glial cells	non-neuronal cells that maintain homeostasis, form myelin and support, protect and provide nutrition to neurons
GLP	good laboratory practice promulgated by the FDA
Homeostasis	the ability of cellular or molecular pathways to seek and maintain a condition of equilibrium or stability within its internal environment when dealing with cellular stress and genetic variation
IDS	iduronate 2-sulfatase, a lysosomal enzyme
IMM	irreversible morbidity or mortality
IND	investigational new drug
IRB	Institutional Review Board
Kinase	an enzyme that catalyzes the addition of a phosphate group to substrates, usually proteins
LRRK2	leucine-rich repeat kinase 2
LSD	lysosomal storage disease
Lysosomal system	the disposal and recycling compartment of a cell, which is involved in the digestion and processing of proteins and lipids in brain cells
MA	Marketing Authorization
MAA	marketing authorization application
Microglial cells	types of glial cells that are the resident macrophages of the brain and spinal cord, and thus act as the first and main form of active immune defense in the central nervous system
MPS II	mucopolysaccharidosis type II, also known as Hunter Syndrome
MSA	multiple system atrophy
NDA	new drug application to the FDA
Neurodegenerative disease	a condition defined by progressive nervous system dysfunction, degeneration and/or death of neurons causing cognitive decline, functional impairment and eventually death
Neurofibrillary tangles	aggregates of hyperphosphorylated Tau protein that are a marker of Alzheimer’s disease and other diseases known as tauopathies
OPTN	Optineurin
Orange Book	Approved Drug Products with Therapeutic Equivalence Evaluations
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic

PK	pharmacokinetic
PK/PD	pharmacokinetic/pharmacodynamic
Proteinopathy	disease that results from disorders of protein synthesis, trafficking, folding, processing or degradation in cells
pRab10	phosphorylation of Rab10 on Threonine 73
pS166	phosphorylation of RIPK1 at Serine 166
pS935	phosphorylation of LRRK2 at Serine 935
Reagent	substance used to characterize or quantify a biological process or component
REMS	Risk Evaluation and Mitigation Strategy
RIPK1	receptor interacting serine/threonine protein kinase 1
RMS	Reference Member State
RMT	receptor-mediated transcytosis
RNA	ribonucleic acid
SPC	summary of product characteristics
TBK	Tank Binding Kinase
TfR	transferrin receptor
TNIP1	TNFAIP3-interacting protein 1
TREM2	triggering receptor expressed in myeloid cells 2
TSPO	translocator protein
TV	transport vehicle

DENALI THERAPEUTICS INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders of Denali Therapeutics Inc.

We have audited the accompanying consolidated balance sheets of Denali Therapeutics Inc. as of December 31, 2016 and 2015, and the related consolidated statements of operations and comprehensive loss, stockholders' (deficit) and cash flows for each of the two years in the period ended December 31, 2016. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. We were not engaged to perform an audit of the Company's internal control over financial reporting. Our audits included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of Denali Therapeutics Inc. at December 31, 2016 and 2015, and the consolidated results of its operations and its cash flows for each of the two years in the period ended December 31, 2016, in conformity with U.S. generally accepted accounting principles.

/s/ Ernst & Young LLP

Redwood City, California
September 8, 2017, except for the second paragraph of Note 1 and for Note 13, as to which the date is December 7, 2017

Denali Therapeutics Inc.

Consolidated Balance Sheets
(In thousands, except share amounts)

	December 31,		Pro Forma Stockholders' Equity as of December 31,
	2015	2016	2016 (Unaudited)
Assets			
Current assets:			
Cash and cash equivalents	$ 30,740	$ 39,853	
Short-term marketable securities	—	138,478	
Prepaid expenses and other current assets	2,691	3,624	
Total current assets	33,431	181,955	
Long-term marketable securities	—	72,580	
Property and equipment, net	3,168	15,262	
Other non-current assets	84	1,270	
Total assets	$ 36,683	$ 271,067	
Liabilities, convertible preferred stock and stockholders' equity (deficit)			
Current liabilities:			
Accounts payable	$ 1,713	$ 1,963	
Accrued liabilities	603	3,850	
Accrued compensation	1,017	2,592	
Deferred rent and other current liabilities	148	701	
Total current liabilities	3,481	9,106	
Deferred rent	18	7,045	
Other non-current liabilities	510	397	
Total liabilities	4,009	16,548	
Commitments and contingencies (Note 7)			
Convertible preferred stock, $0.01 par value; 61,028,466 and 63,288,466 shares authorized as of December 31, 2015 and 2016, respectively; 12,197,880 and 58,600,315 shares issued and outstanding as of December 31, 2015 and 2016, respectively; aggregate liquidation preference of $51,131 and $370,071 as of December 31, 2015 and 2016, respectively; no shares issued and outstanding, pro forma (unaudited)	48,308	348,673	$ —
Stockholders' equity (deficit):			
Common stock, $0.01 par value; 79,527,362 and 83,587,362 shares authorized as of December 31, 2015 and 2016, respectively; 4,260,560 and 8,597,316 shares issued and outstanding, as of December 31, 2015 and 2016, respectively; 67,197,631 shares issued and outstanding, pro forma (unaudited)	170	344	2,688
Additional paid-in capital	1,056	9,387	355,716
Accumulated other comprehensive loss	—	(373)	(373)
Accumulated deficit	(16,860)	(103,512)	(103,512)
Total stockholders' equity (deficit)	(15,634)	(94,154)	254,519
Total liabilities, convertible preferred stock and stockholders' equity (deficit)	$ 36,683	$ 271,067	$ 271,067

See accompanying notes to consolidated financial statements.

Denali Therapeutics Inc.

Consolidated Statements of Operations and Comprehensive Loss
(In thousands, except share and per share amounts)

	Year ended December 31,	
	2015	2016
Operating expenses:		
Research and development	$ 11,571	$ 75,702
General and administrative	5,108	11,731
Total operating expenses	16,679	87,433
Loss from operations	(16,679)	(87,433)
Interest income (expense), net	(109)	781
Net loss	(16,788)	(86,652)
Other comprehensive loss:		
Net unrealized loss on marketable securities, net of tax	—	(373)
Comprehensive loss	$ (16,788)	$ (87,025)
Net loss per share, basic and diluted	$ (5.58)	$ (13.49)
Weighted average number of shares outstanding, basic and diluted	3,006,379	6,424,720
Pro forma net loss per share, basic and diluted (unaudited)		$ (1.77)
Weighted-average number of shares used in computing pro forma net loss per share, basic and diluted (unaudited)		48,924,244

See accompanying notes to consolidated financial statements.

Denali Therapeutics Inc.

Consolidated Statements of Convertible Preferred Stock and Stockholders' (Deficit)
(In thousands, except share amounts)

	Convertible Preferred Stock		Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' (Deficit)
	Shares	Amount	Shares	Amount				
Balance at December 31, 2014	—	$ —	887,324	$ 35	$ —	$ —	$ (70)	$ (35)
Issuance of common stock	—	—	2,815,787	113	(1)	—	(2)	110
Issuance of common stock as consideration in asset acquisition	—	—	472,942	19	581	—	—	600
Issuance of series A-1 convertible preferred stock, net of issuance costs of $484	12,197,880	48,308	—	—	—	—	—	—
Vesting of restricted stock awards	—	—	84,507	3	(3)	—	—	—
Stock-based compensation	—	—	—	—	479	—	—	479
Net loss	—	—	—	—	—	—	(16,788)	(16,788)
Balance at December 31, 2015	**12,197,880**	**48,308**	**4,260,560**	**170**	**1,056**	**—**	**(16,860)**	**(15,634)**
Issuance of series A-1 convertible preferred stock, net of issuance costs of $23	33,916,543	135,643	—	—	—	—	—	—
Issuance of series A-2 convertible preferred stock, net of issuance costs of $7	4,361,527	34,885	—	—	—	—	—	—
Issuance of series B-1 convertible preferred stock, net of issuance costs of $153	8,124,365	129,837	—	—	—	—	—	—
Issuance of common stock as contingent consideration in asset acquisition	—	—	945,880	38	5,242	—	—	5,280
Issuance of common stock upon exercise of stock options	—	—	162,665	6	105	—	—	111
Vesting of early exercised common stock	—	—	239,580	10	153	—	—	163
Vesting of restricted stock awards	—	—	2,988,631	120	(120)	—	—	—
Stock-based compensation	—	—	—	—	2,951	—	—	2,951
Net loss	—	—	—	—	—	—	(86,652)	(86,652)
Other comprehensive loss	—	—	—	—	—	(373)	—	(373)
Balance at December 31, 2016	**58,600,315**	**$348,673**	**8,597,316**	**$ 344**	**$ 9,387**	**$ (373)**	**$ (103,512)**	**$ (94,154)**

See accompanying notes to consolidated financial statements.

Denali Therapeutics Inc.

Consolidated Statements of Cash Flows
(In thousands)

	Year ended December 31, 2015	2016
Operating activities		
Net loss	$(16,788)	$ (86,652)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	121	1,469
Stock-based compensation expense	479	2,951
Non-cash interest expense	110	—
Net amortization of premiums and discounts on marketable securities	—	304
Loss on disposal of property and equipment	—	3
Fair value of common stock issued in connection with asset acquisition	600	5,280
Changes in operating assets and liabilities:		
Restricted cash	(84)	(451)
Prepaid expenses and other assets	(2,691)	(533)
Accounts payable	1,678	161
Accrued and other current liabilities	1,607	5,357
Other non-current liabilities	(84)	(248)
Net cash used in operating activities	(15,052)	(72,359)
Investing activities		
Purchase of marketable securities	—	(226,370)
Purchase of property and equipment	(3,062)	(6,134)
Purchase of other investments	—	(500)
Maturities and sales of marketable securities	—	14,000
Net cash used in investing activities	(3,062)	(219,004)
Financing activities		
Proceeds from convertible promissory note received from a related party	5,000	—
Proceeds from exercise of common stock options	510	111
Proceeds from issuance of common stock	110	—
Proceeds from issuance of convertible preferred stock, net of issuance costs	43,234	300,365
Net cash provided by financing activities	48,854	300,476
Net increase in cash and cash equivalents	30,740	9,113
Cash and cash equivalents at beginning of year	—	30,740
Cash and cash equivalents at end of year	$ 30,740	$ 39,853
Supplemental disclosures of cash flow information		
Convertible preferred stock issuance costs incurred but not yet paid	$ 36	$ —
Property and equipment purchases accrued but not yet paid	$ 126	$ 233
Conversion of convertible promissory note and interest into convertible preferred stock	$ 5,110	$ —

See accompanying notes to consolidated financial statements.

Denali Therapeutics Inc.
Notes to Consolidated Financial Statements

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 degeneration. The Company was incorporated in October 2013 as SPR Pharma Inc. The Company's name was changed to Denali Therapeutics Inc. in March 2015. The Company is headquartered in South San Francisco, California.

Basis of Presentation

These consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("U.S. GAAP"). All share and per share information included in the accompanying consolidated financial statements has been adjusted to reflect a 4-for-1 reverse stock split to be effected prior to the completion of this offering.

Principles of Consolidation

These consolidated financial statements include the accounts of the Company and its wholly-owned subsidiary. This subsidiary was dissolved in September 2016. All intercompany balances and transactions have been eliminated on consolidation.

The Company assesses whether it is the primary beneficiary of a variable interest entity ("VIE") at the inception of the arrangement and at each reporting date. This assessment is based on the Company's power to direct the activities of the VIE that most significantly impact the VIE's economic performance and the Company's obligation to absorb losses or the right to receive benefits from the VIE that could potentially be significant to the VIE.

Unaudited Pro Forma Information

Immediately prior to the completion of this offering, all outstanding shares of convertible preferred stock will automatically convert into common stock. Unaudited pro forma balance sheet information as of December 31, 2016 assumes the conversion of all outstanding convertible preferred stock into shares of common stock. The shares of common stock issuable and the proceeds expected to be received in the initial public offering are excluded from such pro forma financial information. Pro forma basic and diluted net loss per share has been computed to give effect to the conversion of all outstanding convertible preferred stock into shares of common stock. The unaudited pro forma net loss per share does not include the shares expected to be sold and related proceeds to be received from the initial public offering. The unaudited pro forma net loss per share for the year ended December 31, 2016 was computed using the weighted-average number of shares of common stock outstanding, including the pro forma effect of the conversion of all outstanding shares of convertible preferred stock into shares of common stock, as if such conversion had occurred at the beginning of the period, or their issuance dates if later.

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 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 consolidated financial position and results of operations.

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 and marketable securities. Substantially all of the Company's cash and cash equivalents are deposited in accounts with three 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 December 31, 2016, the Company has no off-balance sheet concentrations of credit risk.

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.

Need for Additional Capital

Since inception, the Company has incurred net losses and negative cash flows from operations. During the year ended December 31, 2016, the Company incurred a net loss of $86.7 million and used $72.4 million of cash in operations. At December 31, 2016, the Company had an accumulated deficit of $103.5 million and does not expect to experience positive cash flows in the foreseeable future. The Company has financed its operations to date primarily through the sale and issuance of convertible preferred stock. Management expects to incur additional operating losses in the future as the Company continues the development of, and seeks regulatory approvals for, its product candidates, and begins to commercialize any approved products, and recognizes the need to raise additional capital to fully implement its business plan. The Company intends to raise such capital through public or private equity financings, strategic alliances with third parties and potentially through debt financings. The Company had $250.9 million of cash, cash equivalents and marketable securities at December 31, 2016. Based on the Company's business plans, management believes that this is sufficient to meet its obligations for at least the next twelve months from the issuance date of these consolidated financial statements.

Denali Therapeutics Inc.
Notes to Consolidated Financial Statements

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.

Fair Value of Financial Instruments

ASC Topic 820, Fair Value Measurement ("ASC 820"), establishes a fair value hierarchy for instruments measured at fair value that distinguishes between assumptions based on market data (observable inputs) and the Company's own assumptions (unobservable inputs). Observable inputs are inputs that market participants would use in pricing the asset or liability based on market data obtained from sources independent of the Company. Unobservable inputs are inputs that reflect the Company's assumptions about the inputs that market participants would use in pricing the asset or liability, and are developed based on the best information available in the circumstances.

ASC 820 identifies fair value as the exchange price, or exit price, representing the amount that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. As a basis for considering market participant assumptions in fair value measurements, ASC 820 establishes a three-tier fair value hierarchy that distinguishes between the following:

Level 1 – inputs are quoted prices (unadjusted) in active markets for identical assets or liabilities.

Level 2 – inputs are inputs other than quoted prices included within Level 1 that are observable for the asset or liability, either directly or indirectly.

Level 3 – inputs are unobservable inputs that reflect the Company's own assumptions about the assumptions market participants would use in pricing the asset or liability. Financial assets and liabilities are classified in their entirety based on the lowest level of input that is significant to the fair value measurement.

To the extent that the valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

The carrying amounts reflected in the consolidated balance sheets for cash and cash equivalents, prepaid expenses and other current assets, accounts payable and accrued liabilities approximate their fair values, due to their short-term nature.

Cash and Cash Equivalents

The Company considers all highly liquid investments with original maturities of 90 days or less at the date of purchase to be cash and cash equivalents. Cash equivalents, which consist primarily of highly liquid investments with maturities of three months or less when purchased, are stated at fair value.

Marketable Securities

The Company generally invests its excess cash in money market funds and investment grade short to intermediate-term fixed income securities. Such investments are included in cash and cash

equivalents, short-term marketable securities, or long-term marketable securities on the balance sheets, are considered available-for-sale, and reported at fair value with unrealized gains and losses included as a component of stockholders' deficit. The amortized cost of debt securities is adjusted for amortization of premiums and accretion of discounts to maturity, which is included in interest income (expense), net on the consolidated statements of operations. Realized gains and losses and declines in value judged to be other-than-temporary, if any, on marketable securities are included in interest income (expense), net. The cost of securities sold is determined using specific identification.

The Company periodically evaluates whether declines in fair values of its marketable securities below their book value are other-than-temporary. This evaluation consists of several qualitative and quantitative factors regarding the severity and duration of the unrealized loss as well as the Company's ability and intent to hold the marketable security until a forecasted recovery occurs. Additionally, the Company assesses whether it has plans to sell the security or it is more likely than not it will be required to sell any marketable securities before recovery of its amortized cost basis. Factors considered include quoted market prices, recent financial results and operating trends, implied values from any recent transactions or offers of investee securities, credit quality of debt instrument issuers, other publicly available information that may affect the value of the marketable security, duration and severity of the decline in value, and management's strategy and intentions for holding the marketable security.

Restricted Cash

The Company's restricted cash consists of restricted cash in connection with the building leases for the Company's former and current headquarters. The current portion of $0.1 million is classified within prepaid expenses and other current assets and the non-current portion of $0.5 million is classified within other non-current assets on the accompanying consolidated balance sheets.

Property and Equipment, Net

Property and equipment are stated at cost, net of accumulated depreciation. Depreciation is computed using the straight-line method over the related estimated useful lives as presented in the table below. Significant additions and improvements are capitalized, while repairs and maintenance are charged to expense as incurred.

Leasehold improvements	Shorter of life of asset or lease term
Manufacturing and laboratory equipment	5 years
Computer hardware and software	3 years
Office furniture and equipment	5 years

Impairment of Long-Lived Assets

The Company periodically evaluates property and equipment for impairment whenever events or changes in circumstances indicate that a potential impairment may have occurred. If such events or changes in circumstances arise, the Company compares the carrying amount of the long-lived assets to the estimated future undiscounted cash flows expected to be generated by the long-lived assets. If the estimated aggregate undiscounted cash flows are less than the carrying amount of the long-lived assets, an impairment charge, calculated as the amount by which the carrying amount of the assets exceeds the fair value of the assets, is recorded. The fair value of the long-lived assets is determined based on the estimated discounted cash flows expected to be generated from the long-lived assets. The Company has not recorded any such impairment charges during the years presented.

Denali Therapeutics Inc.
Notes to Consolidated Financial Statements

Deferred Rent

Certain of the Company's operating lease agreements include scheduled rent escalations over the lease term, as well as tenant improvement allowances. Rent expense is charged ratably over the life of the lease. Deferred rent consists of the difference between cash payments and the recognition of rent expense on a straight-line basis for the buildings the Company occupies. Tenant improvement allowances are recorded as a deferred rent liability and are amortized on a straight-line basis over the term of the lease as a reduction to rent expense.

Research and Development Expenses

Research and development costs are expensed as incurred. Research and development costs consist of salaries and other personnel related expenses, including associated stock-based compensation, consulting fees, lab supplies, and facility costs, as well as fees paid to other entities that conduct certain research, development and manufacturing activities on behalf of the Company.

Nonrefundable advance payments for goods and services that will be used or rendered in future research and development activities are deferred and recognized as expense in the period in which the related goods are delivered or services are performed.

The Company has and may continue to acquire the rights to develop and commercialize new product candidates from third parties. The upfront payments to acquire license, product or rights, as well as any future milestone payments, are immediately recognized as research and development expense provided that there is no alternative future use of the rights in other research and development projects.

Stock-Based Compensation

The Company measures employee and director stock-based compensation expense for all stock-based awards at the grant date based on the fair value measurement of the award. The expense is recorded on a straight-line basis over the requisite service period, which is generally the vesting period, for the entire award. Expense is adjusted for actual forfeitures of unvested awards as they occur. The Company calculates the fair value measurement of stock options using the Black-Scholes valuation model.

The Company granted restricted stock awards that vest in conjunction with certain performance and market conditions to certain key employees and directors. At each reporting date, the Company is required to evaluate whether achievement of the performance conditions is probable. Compensation expense is recorded over the appropriate service period based upon the Company's assessment of accomplishing each performance provision.

The Company accounts for stock options issued to non-employees in accordance with the provisions of ASC 505-50, Equity-Based Payments to Non-employees, which requires valuing the stock options on their grant date and remeasuring such stock options at the current fair value at the end of each reporting period until they vest.

Income Taxes

Income taxes are accounted for using the liability method, under which deferred tax assets and liabilities are determined based on the differences between the financial reporting and tax bases of

assets and liabilities and consideration is given to net operating losses and tax credit carryforwards. Deferred tax assets and liabilities are measured using the enacted tax rates that are expected to be in effect when the differences are expected to reverse.

The Company assesses the likelihood that deferred tax assets will be recovered from future taxable income, and a valuation allowance is established when necessary to reduce deferred tax assets to the amounts more likely than not expected to be realized.

The Company recognizes and measures uncertain tax positions using a two–step approach. The first step is to evaluate the tax position taken or expected to be taken by determining whether the weight of available evidence indicates that it is more likely than not that the tax position will be sustained in an audit, including resolution of any related appeals or litigation processes. The second step is to measure the tax benefit as the largest amount that is more than 50% likely to be realized upon ultimate settlement. Significant judgment is required to evaluate uncertain tax positions. The Company evaluates uncertain tax positions on a regular basis. The evaluations are based on a number of factors, including changes in facts and circumstances, changes in tax law, correspondence with tax authorities during the course of the audit, and effective settlement of audit issues.

Comprehensive Loss

Comprehensive loss includes net loss and certain changes in stockholders' deficit that are excluded from net loss, primarily unrealized losses on the Company's marketable securities.

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.

Recent Accounting Pronouncements

In May 2014, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update ("ASU") No. 2014-09 ("ASU 2014-09"), Revenue from Contracts with Customers (Topic 606), and further updated through ASU 2016-12 ("ASU 2016-12"), which amends the existing accounting standards for revenue recognition. ASU 2014-09 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 guidance is effective for annual reporting periods, and interim periods within those years, beginning after December 15, 2017, for public entities and no later than for annual reporting periods beginning after December 15, 2018, for non-public entities. The new revenue standard may be applied retrospectively to each prior period presented or retrospectively with the cumulative effect recognized as of the date of adoption. While the Company continues to assess all potential impacts under ASU 2014-09, it does not believe adopting the new revenue standard will have a material impact on its consolidated financial statements as the Company is not yet generating revenues.

In February 2016, the FASB issued ASU No. 2016-02 ("ASU 2016-02"), Leases (Topic 842), which supersedes the guidance in former ASC 840, Leases. 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. The ASU 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 currently evaluating the impact the adoption of ASU 2016-02 will have on the Company's financial position and results of operations. Management expects that the adoption of this standard will result in the recognition of an asset for the right to use the 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 does not expect a material change to the consolidated statement of operations.

In November 2016, the FASB issued ASU 2016-18, Statement of Cash Flows (Topic 230): Restricted Cash. The purpose of Update No. 2016-18 is to clarify guidance and presentation related to 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. The update is effective for fiscal years beginning after December 15, 2017, including interim reporting periods within those fiscal years. Early adoption is permitted. The Company is currently evaluating the impact of adopting this standard on the consolidated financial statements and disclosures, but does not expect it to be material.

In May 2017, the FASB issued ASU 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. It is effective for annual and interim periods beginning after December 15, 2017. Early adoption is permitted. The Company is currently evaluating the impact of adopting this standard on the consolidated financial statements and disclosures, but does not expect it to have a significant impact.

Denali Therapeutics Inc.
Notes to Consolidated Financial Statements

2. Fair Value Measurements

Assets measured at fair value as of December 31, 2016 are as follows (in thousands):

	Fair Value Measurements			
	Level 1	Level 2	Level 3	Total
Assets:				
Money market funds	$28,705	$ —	$ —	$ 28,705
Short-term:				
U.S. government treasuries	22,268	—	—	22,268
U.S. government agency securities	—	70,787	—	70,787
Corporate debt securities	—	38,941	—	38,941
Commercial paper	—	6,482	—	6,482
Long-term:				
U.S. government treasuries	4,989	—	—	4,989
U.S. government agency securities	—	52,868	—	52,868
Corporate debt securities	—	14,723	—	14,723
Total marketable securities	27,257	183,801	—	211,058
Total fair value measurements	**$55,962**	**$183,801**	**$ —**	**$239,763**

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 year ended December 31, 2016.

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3. Marketable Securities

All marketable securities were considered available-for-sale at December 31, 2016. The amortized cost, unrealized holding gains or losses, and fair value of the Company's marketable securities by major security type at December 31, 2016 are summarized in the table below (in thousands):

	Amortized Cost	Unrealized Holding Gains	Unrealized Holding Losses	Aggregate Fair Value at December 31, 2016
Short-term marketable securities:				
U.S. government treasuries	$ 22,277	$ —	$ (9)	$ 22,268
U.S. government agency securities	70,835	—	(48)	70,787
Corporate debt securities	39,037	—	(96)	38,941
Commercial paper	6,482	—	—	6,482
Total short-term marketable securities	138,631	—	(153)	138,478
Long-term marketable securities:				
U.S. government treasuries	4,996	1	(8)	4,989
U.S. government agency securities	53,005	—	(137)	52,868
Corporate debt securities	14,799	—	(76)	14,723
Total long-term marketable securities	72,800	1	(221)	72,580
Total	**$ 211,431**	**$ 1**	**$ (374)**	**$ 211,058**

As of December 31, 2016, some of the Company's marketable securities were in an unrealized loss position. The Company determined that it did have 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 in the year ended December 31, 2016. All marketable securities with unrealized losses as of December 31, 2016 have been in a loss position for less than twelve months or the loss is not material.

All of the Company's short-term marketable securities have an effective maturity date of less than one year, and all of the Company's long-term marketable securities have an effective maturity of less than two years.

4. Acquisition

In June 2015, the Company acquired Incro Pharmaceuticals Corporation ("Incro"), a preclinical private biotechnology company incorporated in Delaware. The primary asset purchased in the acquisition was an in-process research and development license agreement which would allow the Company to further its RIPK1 program. The Company concluded that the assets acquired and liabilities assumed did not meet the accounting definition of a business as a limited number of inputs were acquired but no processes were acquired, and the licensed technology had not achieved technological feasibility. As such, the acquisition was accounted for as an asset purchase and the Company recorded the purchase price as $1.5 million in research and development expense in the accompanying statement of operations and comprehensive loss in the year ended December 31, 2015.

As purchase consideration the Company issued an aggregate of 472,942 shares of common stock, valued at $0.6 million on the transaction date, to the former Incro stockholders, and recognized

within additional paid-in capital an obligation to issue an additional 27,054 shares of common stock, valued at $32,466, to one former Incro stockholder. The deemed fair value (see Note 10) of the Company's common stock was $1.20 per common share as of the date of the transaction. In addition to the issuance of this equity, the Company assumed liabilities of $0.9 million.

The Company also agreed to issue an additional 945,880 shares of common stock to the former Incro stockholders, and to recognize an obligation to issue 54,110 shares of common stock to one former Incro shareholder ("Milestone Shares"), upon acceptance of an investigational new drug ("IND") application by the U.S. Food and Drug Administration or an equivalent in the EU, Canada, Australia, or New Zealand within six years of the date of the acquisition. Of these shares, 350,000 shares of common stock ("Indemnification Shares") were to be held in escrow by Denali, and would be released to former stockholders of Incro within 30 days of the later of (i) expiration of 18 months after the closing; and (ii) the date the Milestone Shares vest as noted above. The number of Indemnification Shares to be released to Incro's stockholders were to be reduced to the extent of breaches of standard representations by Incro's stockholders. 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.

In August 2016, the Company filed a Clinical Trial Application ("CTA") in Europe to initiate a Phase 1 clinical trial. Upon acceptance of the CTA in September 2016, the issuance of the Milestone Shares was triggered. The Company issued a total of 595,880 shares of common stock, recognized an obligation to issue 54,110 shares of common stock, and recorded a liability for the 350,000 Indemnification Shares held in escrow. The Company recognized $5.3 million of research and development expense related to the estimated fair value of these shares of $5.28 per share during the year ended December 31, 2016. In December 2016, the 350,000 Indemnification Shares were released and issued and the related liability was extinguished upon the expiration of the 18-month period after the closing of the acquisition.

5. License and Collaboration Agreements

F-star

On August 24, 2016, the Company entered into a License and Collaboration Agreement ("Collaboration Agreement") with F-star Gamma Limited ("F-star Gamma"), f-star Biotechnologische Forschungs-und Entwicklungsges m.b.H and F-star Biotechnology Limited (collectively, "F-star"). The goal of the collaboration is the development of certain constant Fc-domains of an antibody with non-native antigen binding activity ("Fcabs"), to enhance delivery of therapeutics across the blood-brain barrier ("BBB") into the brain. The collaboration leverages F-star's modular antibody technology and the Company's expertise in the development of therapies for neurodegenerative diseases.

Under the terms of the Collaboration Agreement, the Company can nominate up to three Fcab targets ("Accepted Fcab Targets"), within the first three years of the date of the Collaboration Agreement; and the Company has selected transferrin receptor ("TfR") as the first Accepted Fcab Target. With respect to each Accepted Fcab Target, the Company can nominate up to eight Fab targets ("Accepted Fab Targets"), which are targets bound by the variable domains of an antibody or other therapeutic modalities ("Fabs"). For each accepted Fcab target, the Company is obligated to use commercially reasonable efforts during the research term to perform development activities in accordance with certain specified development plans. Under the terms of the Collaboration Agreement, the Company received non-exclusive licenses under certain intellectual property to conduct technology

development to discover and develop Fcabs. The Company is obligated to assign to F-star certain patents and know-how that the Company generates under the Collaboration Agreement related to F-star's platform technology or certain Fcabs identified solely by F-star and the Company received a non-exclusive license under certain of F-star Biotechnology's platform patents and know-how to develop and commercialize products in connection with the delivery of therapeutics across the BBB, subject to certain specified restrictions. F-star retains the right to use its intellectual property, including any intellectual property that the Company and F-star jointly own pursuant to the terms of the Collaboration Agreement, outside the scope of the licenses granted to the Company.

Under the terms of the Collaboration Agreement, the Company paid F-star Gamma an upfront fee of $5.5 million, which includes selection of the first Accepted Fcab Target. The Company is obligated to pay a one-time fixed fee in the low single-digit millions for each additional Accepted Fcab Target the Company selects, technical milestone payments for each Accepted Fcab Target, up to a maximum of $15.0 million in the aggregate for all Accepted Fcab Targets, and, at specified times, monthly exclusivity fees for Accepted Fcab Targets and Accepted Fab Targets, which may be eliminated in certain circumstances. The Company is also responsible for certain research costs incurred by F-star 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.

Either party may terminate the agreement if the other party materially breaches the agreement, subject to specified notice and cure provisions, or for the other party's bankruptcy or insolvency. In addition, F-star Gamma may terminate the agreement if the Company challenges any of the patent rights licensed to it by F-star. The Company is able to terminate the agreement for convenience, either in its entirety or on an Accepted Fcab Target-by-Accepted Fcab Target basis or an Accepted Fab Target-by-Accepted Fab Target basis, on 90 days' prior written notice to F-star. Unless earlier terminated, the agreement with F-star will remain in effect until all royalty and milestone payment obligations to F-star Gamma expire.

In connection with the entry into the 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"). The Company must elect whether to exercise its buy-out option before the earlier of (i) dosing of the fifth patient dosed in the first Phase 1 trial of an antibody that binds to an Accepted Fab Target and an Accepted Fcab Target, (ii) the fourth anniversary of the first delivery by F-star of an Fcab meeting certain delivery criteria, and (iii) five and one half years after the delivery by the Company of a notice that it is progressing an Fcab identified from the Company's library that binds to an Accepted Fcab Target. If the Company exercises this buy-out option, it will be obligated to make inital exercise payments ranging from $18.0 million to $50.0 million plus the estimated net cash held by F-star Gamma at the time of such exercise. In addition, it will be required to make certain contingent payments upon the achievement of certain preclinical, clinical, regulatory and commercial milestones, up to a maximum amount of $447.0 million in the aggregate. The amount of the initial exercise and contingent payments varies based on whether F-star delivers an Fcab that meets pre-defined criteria, whether the Fcab has been identified solely by the Company or solely by F-star or jointly by the Company and F-star and the timing of the Company's exercise of the buy-out option. Following exercise of the buy-out option, the Company will not be required to make any further milestone or royalty payments under the Collaboration Agreement. If the Company exercises the buy-out option, then f-star Biotechnologische Forschungs-und Entwicklungsges m.b.H and F-star Biotechnology will continue to be prohibited from developing, commercializing and manufacturing any antibody or other molecule that incorporates any Selected Fcab, or any Selected Fcab as a standalone product, and

from authorizing any third party to take any such action. If the Company does not exercise its option to acquire F-star Gamma prior to the expiration of the buy-out option period, then, from the lapse of the buy-out option period until the Company's rights with respect to an Accepted Fab Target expire or terminate, F-star is prohibited from developing, commercializing and manufacturing any antibody or other molecule that contains both a Selected Fcab and a Fab that specifically binds to the relevant Accepted Fab Target.

If the Company does not exercise the buy-out option, then with respect to each Accepted Fab Target, the Company has the right to obtain from F-star an exclusive, worldwide license to certain intellectual property to develop and commercialize licensed products that contain (i) a Fab that specifically binds to such Accepted Fab Target and (ii) an Fcab that the Company or F-star identifies, either solely or jointly, and that specifically binds to an Accepted Fcab Target, for up to eight Accepted Fab Targets per each Accepted Fcab Target. Each time the Company exercises such license option, it will be obligated to pay F-star Gamma (i) a one-time fixed fee in the low single-digit millions, (ii) milestone payments upon the achievement of certain clinical development and commercial milestones, up to a maximum of $362.5 million in the aggregate; (iii) additional sales-based milestones if net sales of licensed products achieve certain specified levels, up to a maximum amount payable to F-star of $650.0 million in the aggregate and (iv) low-to-mid single-digit percentage royalties on net sales of licensed products. Such amounts may be reduced by a specified percentage depending on the origin of the Fcab incorporated in the applicable licensed product and whether F-star delivers to the Company an Fcab that meets pre-defined criteria. The Company has the right to credit a certain amount of royalty payments that it pays to third parties with respect to certain licensed products against the Company's royalty obligation to F-star Gamma, 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) the expiration of the last valid claim of a licensed patent covering such licensed product in such country, (b) the expiration of regulatory exclusivity for such licensed product in such country and (c) the twelfth anniversary of the first commercial sale of such licensed product in such country.

The Company recognized the upfront option fee of $0.5 million within other non-current assets recorded at cost. This asset will be assessed for potential impairment on an ongoing basis. No impairment charge was recognized during the year ended December 31, 2016.

The Company determined that F-star Gamma is and continues to be a variable interest entity and that the Company holds a variable interest in F-star Gamma's intellectual property assets and the related potential future product candidates these assets may produce through the Collaboration Agreement and the Option Agreement. However, the Company concluded that its governance role in the collaboration, which is specified by the terms of a joint steering committee, does not provide the Company the power to direct the activities of F-star Gamma that most significantly impact F-star Gamma's economic performance. Based on this conclusion, the Company is not considered to be the primary beneficiary of F-star Gamma; and therefore F-star Gamma is not subject to consolidation by the Company.

The Company recognized the entirety of the $5.5 million upfront license fee in research and development expense for the year ended December 31, 2016. The Company recognized an additional $0.3 million of research and development expense related to the funding of F-star Gamma research costs during the year ended December 31, 2016.

The $0.5 million other non-current asset is the only asset or liability recorded in the Company's consolidated balance sheet that relates to the Company's variable interest in F-star Gamma at

December 31, 2016. The upfront payments of $0.5 million and $5.5 million, along with 1) the obligation to fund certain future research costs, 2) any future Fcab selection fee, technical milestone payments or monthly exclusivity fees and 3) any future license fees or pre-commercial milestone payments represent the Company's maximum exposure to loss under the arrangements with F-star. The ultimate expense that the Company incurs under the arrangements with F-Star cannot be quantified at this time as the amount will vary based on the timing and outcome of future research activities.

Genentech

On June 17, 2016, the Company entered into an Exclusive License Agreement with Genentech, Inc. ("Genentech"). The agreement gives the Company access to Genentech's preclinical stage LRRK2 small molecule program, which can be used to enhance and further progress the Company's in-house LRRK2 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 are included in research and development expense for the year ended December 31, 2016 as there is no alternative future use of the rights acquired in other research and development projects.

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.

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.

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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.

6. Balance Sheet Components:

Property and Equipment, Net

	December 31,	
	2015	2016
	(in thousands)	
Lab equipment	$3,034	$ 8,868
Leasehold improvements	101	7,543
Computers equipment and purchased software	146	373
Furniture and fixtures	8	66
	3,289	16,850
Less: accumulated depreciation	(121)	(1,588)
Total property and equipment, net	$3,168	$15,262

Depreciation expense was $0.1 million and $1.5 million for the years ended December 31, 2015 and 2016, respectively.

Prepaid Expenses and Other Current Assets

	December 31,	
	2015	2016
	(in thousands)	
Prepaid research and development expenses	$1,652	$2,396
Accrued interest on short-term marketable securities	—	438
Prepaid employee bonuses	973	234
Other prepaid and current assets	66	556
Total prepaid expenses and other current assets	$2,691	$3,624

Other Non-Current Assets

	December 31,	
	2015	2016
	(in thousands)	
Other investments	$—	$ 500
Restricted cash	84	451
Other prepaid and non-current assets	—	319
Total other non-current assets	$ 84	$1,270

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Deferred Rent and Other Current Liabilities

	December 31,	
	2015	2016
	(in thousands)	
Current portion of deferred rent liability	$ —	$538
Other current liabilities	148	163
Total deferred rent and other current liabilities	$148	$701

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 ("Headquarters Lease"). The Headquarters Lease commenced on August 1, 2016 with a lease term of eight years. The Company has an option to extend the lease term for a period of five 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 original expiration of the lease term. The Headquarters Lease provides for monthly base rent amounts escalating over the term of the lease. In addition, the Headquarters Lease provides both a tenant improvement allowance ("TIA") of up to $7.4 million, of which $1.9 million will 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 results in an increase of base rent of $0.4 million per year.

The Company utilized $0.1 million and $7.3 million of the TIA in the years ended December 31, 2015 and 2016, respectively. The total $7.4 million TIA has been recorded as leasehold improvements and deferred rent liability on the consolidated balance sheet. 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 lease term. Under the terms of the Headquarters Lease, the Company was required to pay a security deposit of $0.5 million, which is recorded as other non-current assets in the accompanying consolidated balance sheets.

In May 2015, the Company entered into a non-cancelable operating lease for office and research and development space in South San Francisco that expires in December 2017 (the "First Lease"). The First Lease provides for 9,855 of rentable square feet at a base rent that increases annually. Under the terms of the First Lease, the Company was required to pay a security deposit of $0.1 million, which is recorded as prepaid expenses other current assets in the accompanying consolidated balance sheets.

On July 22, 2016, the Company entered into a sublease agreement with a third party for the entirety of the remaining term of the First Lease. The sublease commenced on August 22, 2016. The Company received sublease payments totaling $0.1 million through the year ended December 31, 2016 and expects to receive future minimum payments from this sublease of $0.4 million in 2017, which is recognized as an offset to rent expense.

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.

Rent expense for the years ended December 31, 2015 and 2016 was $0.2 million and $1.0 million, respectively.

As of December 31, 2016, the future minimum lease payments under non–cancelable operating leases are as follows (in thousands):

Year Ended December 31:	
2017	$ 2,510
2018	2,586
2019	2,664
2020	2,745
2021 and later	10,534
	$21,039

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

In the normal course of business, the Company enters into various firm purchase commitments primarily related to research and development activities. As of December 31, 2016, the Company has non-cancelable purchase commitments of $1.0 million and contractual obligations under license agreements of $0.2 million. Pursuant to certain license and collaboration agreements, the Company has obligations to make future milestone and royalty payments to other third parties. However, because these amounts are contingent and not fixed or determinable, they have not been included on the Company's consolidated balance sheet.

8. Convertible Promissory Note

In January 2015, the Company entered into a convertible promissory note with a related party, a stockholder of the Company. The principal amount of the promissory note was $5.0 million at a fixed

interest rate of 8.0%, which was repayable in January 2016. Interest of $0.1 million accrued on the note and was recognized within interest income (expense), net in the consolidated statement of operations and comprehensive loss in the year ended December 31, 2015.

The entire amount due, including interest, was converted into 1,277,397 shares of Series A-1 convertible preferred stock in May 2015 (see Note 9).

9. Convertible Preferred Stock and Stockholders' Deficit

Convertible Preferred Stock

The Company is authorized to and has issued two classes of stock: convertible preferred stock and common stock. Convertible preferred stock is carried at the issuance price, net of issuance costs. The carrying value of the convertible preferred stock has not been accreted up to its redemption value as no redemption events are considered probable by management.

The Company entered into a preferred stock purchase agreement ("Preferred Stock Purchase Agreement"), with certain investors on May 8, 2015 (the "Initial Closing"), under which the Company agreed to sell up to 45,223,973 shares of Series A-1 convertible preferred stock and 4,361,532 shares of Series A-2 convertible preferred stock. Additionally, at the Initial Closing, the Company concurrently issued 6,295,805 shares of Series A-1 convertible preferred stock for net proceeds of $24.8 million.

The Preferred Stock Purchase Agreement provided that, upon Board of Directors approval, each investor would purchase its pro-rata portion of the shares to be issued in one or more additional series A-1 closings, and in any Series A-2 closings. Further, the Company agreed to sell and issue said shares of Series A-1 convertible preferred stock on the same terms as the first tranche, and to issue said shares of Series A-2 convertible preferred stock on the terms included in the Preferred Stock Purchase Agreement. The second and third Series A-1 closings added further obligations for new investors to participate in the Series A-2 tranches. The Company did not separately account for tranche purchase rights described above as they were not freestanding from the associated shares of convertible preferred stock.

On May 20, 2015 (the "First Additional Closing") the Company and the Series A convertible preferred stock shareholders amended the Preferred Stock Purchase Agreement pursuant to which the Company agreed to sell up to an additional 456,250 shares of Series A-1 convertible preferred stock. Additionally, at the First Additional Closing, the Company issued 3,481,250 shares of Series A-1 convertible preferred stock for net proceeds of $13.9 million and on July 22, 2015 ("Second Additional Closing"), the Company issued an additional 2,420,825 shares of Series A-1 convertible preferred stock for net proceeds of $9.6 million.

On January 6, 2016 (the "Third Additional Closing"), the Company issued 500,000 shares of Series A-1 convertible preferred stock, for net proceeds of $2.0 million. On January 26, 2016 (the "first Tranche Closing"), the Company issued 11,249,997 shares of Series A-1 convertible preferred stock, for net proceeds of $45.0 million. On June 6, 2016 (the "Second Tranche Closing and Series A-2 Closing"), the Company issued 22,166,546 shares of Series A-1 convertible preferred stock and 4,361,527 shares of Series A-2 convertible preferred stock, for net proceeds of $88.7 million and $34.9 million, respectively. All of these shares were sold under the Preferred Stock Purchase Agreement.

On June 23, 2016 (the "First Series B-1 Closing"), the Company entered into a preferred stock purchase agreement ("Series B Preferred Stock Purchase Agreement") with certain investors, under

which the Company sold 7,646,241 shares of Series B-1 convertible preferred stock at a price of $16.00 per share for net proceeds of $122.2 million. In connection with this financing, the Company amended and restated its certificate of incorporation to increase the authorized shares of its common stock to 81,787,362 shares and the authorized shares of its preferred stock to 63,288,466 shares, each with a par value of $0.01 per share. The authorized preferred shares consisted of 46,114,433 designated as Series A-1 convertible preferred stock, 4,361,533 designated as Series A-2 convertible preferred stock, 8,125,000 designated Series B-1 convertible preferred stock and 4,687,500 designated Series B-2 convertible preferred stock.

On August 26, 2016, (the “Second Series B-1 Closing”), the Company sold 478,124 shares of Series B-1 convertible preferred stock at a price of $16.00 per share for net proceeds of $7.6 million.

On December 23, 2016, upon the passing of six months from the First Series B-1 Closing, the shares authorized for Series B-2 were no longer available for issuance under the Series B Preferred Stock Purchase Agreement.

At December 31, 2015, convertible preferred stock consisted of the following (in thousands, except share and per share amounts):

	Shares Authorized	Shares Issued and Outstanding	Issuance Price per Share	Carrying Value	Liquidation Preference
Series A-1	46,114,433	12,197,880	$ 4.00	$48,308	$ 51,131
Series A-2	4,361,533	—	8.00	—	—
Series B	10,552,500	—	16.00	—	—
	61,028,466	12,197,880		$48,308	$ 51,131

At December 31, 2016, convertible preferred stock consisted of the following (in thousands, except share and per share amounts):

	Shares Authorized	Shares issued and Outstanding	Issuance Price per Share	Carrying Value	Liquidation Preference
Series A-1	46,114,433	46,114,423	$ 4.00	$183,951	$198,264
Series A-2	4,361,533	4,361,527	8.00	34,885	36,483
Series B-1	8,125,000	8,124,365	16.00	129,837	135,324
Series B-2	4,687,500	—	—	—	—
	63,288,466	58,600,315		$348,673	$370,071

The rights, preferences and privileges of the convertible preferred stock are as follows:

Dividend Rights

The holders of preferred stock are entitled to receive dividends, if and when declared by the Board of Directors, at the rate of $0.08 per share per annum for Series A-1, $0.16 per share per annum for Series A-2, and $0.32 per share per annum for Series B-1 from and after the date of issuance of such shares, subject to adjustment in the event of a stock split, combination, common stock dividend or distribution, reclassification, exchange, substitution or reorganization. As of December 31, 2015 and 2016, no such dividends had been declared or accrued.

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Dividends on any other class of capital stock cannot be paid unless the holders of the preferred stock first receive, or simultaneously receive, the preferred stock dividend. The holders of preferred stock also participate in dividends paid on common stock as if the shares of preferred stock had been converted into shares of common stock and are considered participating securities.

Conversion Rights

The holders of preferred stock have the right to convert at any time into shares of common stock initially at a one-for-one ratio. All shares of the preferred stock shall be automatically converted into shares common stock (i) upon the consent of the holders of at least a majority of the outstanding preferred stock, or (ii) upon the closing of a firmly underwritten initial public offering of common stock at a price of at least $5.00 per share resulting in at least $50.0 million of gross proceeds. The conversion price for each series of preferred stock is subject to an adjustment in the event of stock split, combination, common stock dividend or distribution, reclassification, exchange, substitution, or reorganization.

Liquidation Rights

In the event of any voluntary or involuntary liquidation, dissolution or winding up of the Company or a deemed liquidation event, the holders of shares of preferred stock then outstanding are entitled to be paid out of the assets of the Company available for distribution to its stockholders, before any payment can be made to the holders of common stock, an amount per share equal to the greater of (i) the original issue price for the Series of preferred stock held plus any dividends accrued but unpaid, whether or not declared; or (ii) such amount per share as would have been paid if all shares of preferred stock had been converted to common stock immediately prior to such liquidation, dissolution, winding up or deemed liquidation event. If assets of the Company available are insufficient to pay holders of Preferred Stock the full amount they are entitled to, the holders of preferred stock will share ratably in any distribution of the assets available for distribution in proportion to the amounts due such holders. After the payment of all preferential amounts required to be paid to the holders of shares of preferred stock, the remaining assets of the Company will be distributed among the holders of the shares of common stock, pro rata based on the number of shares held by each such holder.

The Company classifies its convertible preferred stock outside of stockholders' deficit as certain change in control events are outside the Company's control.

Voting Rights

Each share of preferred stock has voting rights equal to the number of shares of common stock into which the preferred stock could be converted immediately after the close of business on the record date.

As long as certain investors in Series A convertible preferred stock hold 100,000 or more shares of convertible preferred stock purchased pursuant to the Preferred Stock Purchase Agreement, subject to adjustment in the event of a stock split, combination, common stock dividend or distribution, reclassification, exchange, substitution or reorganization. They are entitled to elect individually one member of the Board totaling five Series A Directors. Series B convertible preferred stockholders are entitled to elect one member of the Board by majority vote of the Series B convertible preferred stockholders. Together, Series A and Series B convertible preferred stock investors shall be entitled to elect two additional members of the Board that are not otherwise an affiliate of the Company or of any investor.

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Notes to Consolidated Financial Statements

Redemption

Upon certain change in control events that are outside of the Company's control, including liquidation, sale or transfer of control of the Company, holders of the convertible preferred stock can cause its redemption. Shares of preferred stock must be redeemed by the Company at the original issue price for each series of preferred stock plus any dividends accrued but unpaid, whether or not declared, in three annual installments, upon a written request from the holders of a majority of the then outstanding shares of preferred stock, which request can be made at any time after the fifth anniversary of the Series B-1 original issue date (on or after June 22, 2021). On each of the three annual redemption dates the Company must redeem the number of outstanding shares of preferred stock determined by dividing the total number of outstanding shares of preferred stock by the number of remaining redemption dates.

Common Stock

As of December 31, 2016, the Company had reserved shares of common stock for issuance as follows:

Series A-1 convertible preferred stock	46,114,433
Series A-2 convertible preferred stock	4,361,533
Series B-1 convertible preferred stock	8,125,000
Series B-2 convertible preferred stock	4,687,500
Options issued and outstanding	5,374,014
Restricted shares subject to future vesting	3,922,638
Early exercised common stock subject to future vesting	510,417
Options available for future grants	1,813,321
Shares to be issued under Incro acquisition agreement	81,164
Total	74,990,020

10. Stock Incentive Plan

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, non-qualified 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 incentive stock options and non-statutory 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

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' deficit 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.

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Notes to Consolidated Financial Statements

In 2015, there were 750,000 options exercised prior to vesting for total proceeds of $0.5 million to the Company which was recognized as a long-term liability as of December 31, 2015. No shares vested relating to these exercises in the year ended December 31, 2015. The Company reclassified $0.2 million to stockholders' deficit upon vesting during the year ended December 31, 2016 and the remaining proceeds related to the unvested options of $0.3 million as of December 31, 2016 will be reclassified to stockholders' deficit as the options vest.

As of December 31, 2015 and 2016, there were 2,024,871 shares and 1,813,321 shares, respectively, available for the Company to grant under the 2015 Plan.

Stock Option Activity

The following table summarizes option activity under 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, 2014	—	$ —	—	
Options granted	4,275,121	0.68		
Options exercised	(750,000)	0.68		
Balance at December 31, 2015	3,525,121	0.68	9.73	
Options granted	2,112,808	3.45		
Options exercised	(162,665)	0.68		
Options forfeited	(101,250)	0.82		
Balance at December 31, 2016	5,374,014	$ 1.77	9.03	$ 18,873
Options vested and expected to vest at December 31, 2016	3,629,276	$ 2.29	9.21	$ 10,847
Options exercisable at December 31, 2016	419,085	$ 0.68	8.83	$ 1,926

Aggregate intrinsic value represents the difference between the Company's estimated fair value of its common stock and the exercise price of outstanding options. The total intrinsic value of options exercised was $0.4 million and $0.7 million for the years ended December 31, 2015 and 2016, respectively. The total intrinsic value of options exercisable was $1.9 million as of December 31, 2016. During the year ended December 31, 2016, the weighted-average grant-date fair value of the options vested was $1.36 per share. No options vested during the year ended December 31, 2015. The weighted-average grant date fair value of options granted during the years ended December 31, 2015 and 2016 was $2.03 and $2.83 per share, respectively.

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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:

	Year Ended December 31,	
	2015	2016
Expected term (in years)	6.08	6.00-6.08
Volatility	85.7%-90.2%	91.2%-92.2%
Risk-free interest rate	1.7%-1.9%	1.2%-2.1%
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 used 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 any trading history for its common stock.

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.

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.

Performance Contingent Stock Options Granted to Employees

In August and November 2015, the Board of Directors granted 250,000 and 500,000 of stock option awards to certain executive officers, respectively. These awards have an exercise price of $0.68 per share. These awards vest over time and include a performance provision which states that upon the occurrence of a change in control event, the vesting term would accelerate. As of December 31, 2016, the Company determined that the achievement of the requisite performance condition was not probable and, as a result, the expense relating to these grants is being recognized over the initial time-based vesting period. If the performance goal is ever deemed to be probable of achievement, the recognition of compensation expense will be accelerated in accordance with the accelerated vesting schedule.

The estimated fair value of employee performance-contingent options was estimated at the date of grant using a Black-Scholes option-pricing model using the same assumptions as the Stock Options Granted to Employees with Service-based Vesting Valuation Assumptions.

Performance and Market Contingent Stock Options Granted to Employees

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

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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 vesting 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. As of December 31, 2016, the Company determined that the achievement of the requisite performance conditions was not probable and, as a result, no compensation cost was recognized for 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

Stock-based compensation related to stock options granted to non-employees is recognized as the stock options are earned. The estimated fair value of the stock options granted is calculated at each reporting date using the Black-Scholes option-pricing model with the following assumptions:

	Year Ended December 31,	
	2015	2016
Expected term (in years)	9.50-9.84	8.50-9.70
Volatility	88.6%-89.3%	95.3%-98.2%
Risk-free interest rate	2.0%-2.3%	2.4%
Dividend yield	—	—

The expected term for stock options granted to non-employees is equivalent to the remaining contractual term of the award.

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Restricted Stock Activity

The following table summarizes restricted stock activity:

	Shares	Weighted-Average Fair Value at Date of Grant per Share
Unvested at December 31, 2015	6,911,269	$ 0.18
Granted	—	—
Vested	(2,988,631)	0.17
Forfeited	—	—
Unvested at December 31, 2016	3,922,638	$ 0.18

At December 31, 2016, there was $0.7 million of total unrecognized compensation cost related to non-vested restricted stock, all which is expected to be recognized over a remaining weighted-average period of 2.5 years.

Stock-Based Compensation Expense

The Company's results of operations include expenses relating to employee and non-employee stock-based awards and restricted stock awards as follows (in thousands):

	Year Ended December 31,	
	2015	2016
Research and development	$ 94	$ 2,078
General and administrative	385	873
Total	$ 479	$ 2,951

As of December 31, 2016, total unamortized stock-based compensation expense related to unvested employee and non-employee awards that are expected to vest was $7.2 million and $0.4 million, respectively. The weighted-average period over which such stock-based compensation expense will be recognized is approximately 3.1 years and 3.2 years as of December 31, 2015 and 2016, respectively.

The Company recorded stock-based compensation expense for options issued to non-employees under the 2015 Plan of $0.1 million and $1.0 million for the years ended December 31, 2015 and 2016, respectively.

11. Income Taxes

The Company has incurred net operating losses for all the periods presented. The Company has not reflected any benefit of such net operating loss carryforwards in the accompanying financial statements. The Company has established a full valuation allowance against its deferred tax assets due to the uncertainty surrounding the realization of such assets.

The effective tax rate for the years ended December 31, 2015 and 2016 is different from the federal statutory tax rate primarily due to the valuation allowance against deferred tax assets as a

result of insufficient sources of income. The effective tax rate of the provision for income taxes differs from the federal statutory rate as follows:

	Year Ended December 31,	
	2015	2016
Taxes at the U.S. statutory tax rate	34.0%	34.0%
Change in valuation allowance	(34.1)	(32.0)
Contingent consideration issued in tax-free reorganization	—	(2.1)
Research tax credits	1.5	0.6
Stock-based compensation	(0.2)	(0.5)
Other	(1.2)	—
Total provision for income taxes	0.0%	0.0%

The components of the Company's net deferred tax assets are as follows (in thousands):

	December 31,	
	2015	2016
Deferred tax assets:		
Net operating loss carryforwards	$ 4,452	$ 26,044
Tax credit carryforwards	410	1,486
Reserves and accruals	370	4,038
Capitalized start-up costs	1,987	5,128
Intangibles	—	6,565
Share based compensation	67	390
Gross deferred tax assets	7,286	43,651
Valuation allowance	(6,823)	(40,113)
Net deferred tax assets	463	3,538
Deferred tax liabilities:		
Property and equipment	(65)	(3,379)
Stock-based compensation	(398)	(159)
Net deferred tax assets	$ —	$ —

Recognition of deferred tax assets is appropriate when realization of such assets is more likely than not. Based upon the weight of available evidence, especially the uncertainties surrounding the realization of deferred tax assets through future taxable income, the Company believes it is not more likely than not that the deferred tax assets will be fully realizable. Accordingly, the Company has provided a 100% valuation allowance against its net deferred tax assets as of December 31, 2015 and 2016.

As of December 31, 2016, the Company has federal net operating loss ("NOL") carryforwards of approximately $65.4 million, which are available to reduce future taxable income, and has federal tax credits of approximately $1.2 million which may be used to offset future tax liabilities. The federal NOL and federal tax credit carryforwards will begin to expire in 2035. The Company also has state NOL carryforwards of approximately $65.4 million, which are available to reduce future taxable income, and has state tax credits of approximately $1.4 million which may be used to offset future tax liabilities. The state NOL will begin to expire in 2035 and the state tax credit carryforwards will be carried forward

indefinitely. The NOL and tax credit carryforwards are subject to review and possible adjustment by the Internal Revenue Service ("IRS") and state tax authorities and may become subject to an annual limitation in the event of certain future cumulative changes in the ownership interest of significant stockholders over a three-year period in excess of 50%, as defined under Sections 382 and 383 of the Internal Revenue Code of 1986. This could limit the amount of tax attributes that can be utilized annually to offset future taxable income or tax liabilities.

The Company follows the provisions of ASC 740, Accounting for Income Taxes, and the accounting guidance related to accounting for uncertainty in income taxes. The Company determines its uncertain tax positions based on a determination of whether and how much of a tax benefit taken by the Company in its tax filings is more likely than not to be sustained upon examination by the relevant income tax authorities.

A reconciliation of the beginning and ending amounts of unrecognized tax benefits is as follows (in thousands):

	December 31,	
	2015	2016
Gross unrecognized tax benefits at January 1	$ —	$ 122
Additions for tax positions taken in a prior year	—	7
Additions for tax positions taken in the current year	122	411
Reductions for tax positions taken in the prior year	—	(9)
Gross unrecognized tax benefits at December 31	$ 122	$ 531

If recognized, none of the unrecognized tax benefits as of December 31, 2015 and 2016 would reduce the annual effective tax rate, primarily due to corresponding adjustments to the valuation allowance. The Company will recognize both accrued interest and penalties related to unrecognized benefits in income tax expense. As of December 31, 2016, no liability has been recorded for potential interest or penalties. The Company does not expect the unrecognized tax benefits to change significantly over the next 12 months.

Since the Company is in a loss carryforward position, the Company is generally subject to examination by the U.S. federal, state and local income tax authorities for all tax years in which a loss carryforward is available.

12. Net Loss and Unaudited Pro Forma 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):

	Year Ended December 31,	
	2015	2016
Numerator:		
Net loss	$ (16,788)	$ (86,652)
Denominator:		
Weighted average common shares outstanding	3,006,379	6,424,720
Net loss per share, basic and diluted	$ (5.58)	$ (13.49)

Denali Therapeutics Inc.
Notes to Consolidated Financial Statements

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 common shares 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:

	December 31,	
	2015	2016
Series A-1 convertible preferred stock	12,197,880	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	3,525,121	5,374,014
Restricted shares subject to future vesting	6,911,269	3,922,638
Early exercised common stock subject to future vesting	750,000	510,417
Shares to be issued under Incro acquisition agreement	27,054	81,164
Total	23,411,324	68,488,548

Unaudited Pro Forma Net Loss Per Share

The following table sets forth the computation of the Company's unaudited pro forma basic and diluted net loss per share (in thousands, except for share and per share amounts):

	Year ended December 31, 2016 (Unaudited)
Net loss	$ (86,652)
Shares used in computing net loss per share, basic and diluted	6,424,720
Pro forma adjustment to reflect assumed conversion of preferred stock	42,499,524
Shares used to compute pro forma net loss per share, basic and diluted	48,924,244
Pro forma net loss per share, basic and diluted	$ (1.77)

13. Subsequent event

In November 2017, the Company sold 1,764,705 shares of Series B-2 convertible preferred stock at a price of $17.00 per share for net proceeds of $29.9 million. In connection with this financing, the Company amended and restated its certificate of incorporation to reflect that the holders of preferred stock are entitled to receive dividends, if and when declared by the Board of Directors, at the rate of $0.34 per share per annum, and to establish the Series B-2 original issuance price at $4.25 per share, both subject to adjustment in the event of a stock split, combination, common stock dividend or distribution, reclassification, exchange, substitution, or reorganization. The amendments provided for rights, preferences and privileges for the Series B-2 convertible preferred stock similar to those of the Series A-1, A-2 and B-1 convertible preferred stock described in Note 9, Convertible Preferred Stock and Stockholders' Deficit.

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Condensed Consolidated Balance Sheets
(In thousands, except share and per share amounts)

	December 31, 2016	September 30, 2017 (Unaudited)	Pro Forma Stockholders' Equity as of September 30, 2017 (Unaudited)
Assets			
Current assets:			
Cash and cash equivalents	$ 39,853	$ 36,269	
Short-term marketable securities	138,478	149,532	
Prepaid expenses and other current assets	3,624	2,442	
Total current assets	181,955	188,243	
Long-term marketable securities	72,580	4,975	
Property and equipment, net	15,262	14,635	
Other non-current assets	1,270	2,456	
Total assets	$ 271,067	$ 210,309	
Liabilities, convertible preferred stock and stockholders' equity (deficit)			
Current liabilities:			
Accounts payable	$ 1,963	$ 2,270	
Accrued liabilities	3,850	4,116	
Accrued compensation	2,592	2,865	
Deferred rent and other current liabilities	701	903	
Total current liabilities	9,106	10,154	
Deferred rent	7,045	6,519	
Other non-current liabilities	397	499	
Total liabilities	16,548	17,172	
Commitments and contingencies (Note 6)			
Convertible preferred stock, $0.01 par value; 63,288,466 shares authorized as of December 31, 2016 and September 30, 2017 (unaudited); 58,600,315 shares issued and outstanding as of December 31, 2016 and September 30, 2017 (unaudited); aggregate liquidation preference of $390,974 as of September 30, 2017 (unaudited); no shares issued and outstanding, pro forma (unaudited)	348,673	348,673	$ —
Stockholders' equity (deficit):			
Common stock, $0.01 par value; 83,587,362 shares authorized as of December 31, 2016 and September 30, 2017 (unaudited); 8,597,316 and 10,607,828 shares issued and outstanding as of December 31, 2016 and September 30, 2017 (unaudited), respectively; 69,208,143 shares issued and outstanding, pro forma (unaudited)	344	424	2,768
Additional paid-in capital	9,387	13,087	359,416
Accumulated other comprehensive loss	(373)	(237)	(237)
Accumulated deficit	(103,512)	(168,810)	(168,810)
Total stockholders' equity (deficit)	(94,154)	(155,536)	193,137
Total liabilities, convertible preferred stock and stockholders' equity (deficit)	$ 271,067	$ 210,309	$ 210,309

See accompanying notes to condensed consolidated financial statements.

Denali Therapeutics Inc.

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

	Nine Months Ended September 30,	
	2016	2017
Operating expenses:		
Research and development	$ 58,972	$ 55,989
General and administrative	8,685	10,611
Total operating expenses	67,567	66,600
Loss from operations	(67,567)	(66,600)
Interest income, net	359	1,302
Net loss	(67,298)	(65,298)
Other comprehensive income (loss):		
Net unrealized gain (loss) on marketable securities, net of tax	(131)	136
Comprehensive loss	$ (67,429)	$ (65,162)
Net loss per share, basic and diluted	$ (11.43)	$ (6.77)
Weighted average number of shares outstanding, basic and diluted	5,888,385	9,643,686
Pro forma net loss per share, basic and diluted		$ (0.96)
Weighted-average number of shares used in computing pro forma net loss per share, basic and diluted		68,244,028

See accompanying notes to condensed consolidated financial statements.

Denali Therapeutics Inc.

Condensed Consolidated Statements of Cash Flows
(Unaudited)
(In thousands)

	Nine Months Ended September 30,	
	2016	2017
Operating activities		
Net loss	$ (67,298)	$ (65,298)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation	783	2,275
Stock-based compensation expense	2,260	2,952
Net amortization of premiums and discounts on marketable securities	144	899
Loss on disposal of property and equipment	—	1
Fair value of common stock issued in connection with asset acquisition	5,280	—
Changes in operating assets and liabilities:		
Restricted cash	(451)	—
Prepaid expenses and other assets	769	(3)
Accounts payable	1,592	318
Accrued and other current liabilities	3,077	884
Other non-current liabilities	(149)	(327)
Net cash used in operating activities	(53,993)	(58,299)
Investing activities		
Purchase of marketable securities	(195,736)	(46,651)
Purchase of property and equipment	(3,821)	(1,804)
Purchase of other investments	(500)	—
Maturities and sales of marketable securities	—	102,438
Net cash provided by (used in) investing activities	(200,057)	53,983
Financing activities		
Proceeds from exercise of common stock options	114	732
Proceeds from issuance of convertible preferred stock, net of issuance costs	300,366	—
Net cash provided by financing activities	300,480	732
Net increase (decrease) in cash and cash equivalents	46,430	(3,584)
Cash and cash equivalents at beginning of period	30,740	39,853
Cash and cash equivalents at end of period	$ 77,170	$ 36,269
Supplemental disclosures of cash flow information		
Convertible preferred stock issuance costs incurred but not yet paid	$ 27	$ —
Property and equipment purchases accrued but not yet paid	$ 1,938	$ 78
Deferred IPO costs accrued but not yet paid	$ —	$ 1,136

See accompanying notes to condensed consolidated financial statements.

Denali Therapeutics Inc.
Notes to Unaudited Interim Condensed Consolidated Financial Statements

1. Significant Accounting Policies

Organization and Description of Business

Denali Therapeutics Inc. (the "Company") is a biopharmaceutical company, incorporated in Delaware, that discovers and develops therapeutics to defeat neurodegenerative diseases. The Company was incorporated in October 2013 as SPR Pharma Inc. The Company's name was changed to Denali Therapeutics Inc. in March 2015. The Company is headquartered in South San Francisco, California.

Basis of Presentation

These consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("U.S. GAAP"). All share and per share information included in the accompanying consolidated financial statements has been adjusted to reflect a 4-for-1 reverse stock split to be effected prior to the completion of this offering.

Principles of Consolidation

These consolidated financial statements include the accounts of the Company and its wholly-owned subsidiary. This subsidiary was dissolved in September 2016. All intercompany balances and transactions have been eliminated on consolidation.

The Company assesses whether it is the primary beneficiary of any variable interest entity ("VIE") in which it has a variable interest at the inception of the arrangement and at each reporting date. This assessment is based on the Company's power to direct the activities of the VIE that most significantly impact the VIE's economic performance and the Company's obligation to absorb losses or the right to receive benefits from the VIE that could potentially be significant to the VIE.

Unaudited Interim Consolidated Financial Statements

The interim condensed consolidated balance sheet as of September 30, 2017, and the statements of operations and comprehensive loss, and cash flows for the nine months ended September 30, 2016 and 2017 are unaudited. The unaudited interim consolidated financial statements have been prepared on the same basis as the annual consolidated financial statements and reflect, in the opinion of management, all adjustments of a normal and recurring nature that are necessary for the fair presentation of the Company's financial position as of September 30, 2017 and its results of operations and cash flows for the nine months ended September 30, 2016 and 2017. The financial data and the other financial information disclosed in these notes to the consolidated financial statements related to the nine-month periods are also unaudited. The consolidated results of operations for the nine months ended September 30, 2017 are not necessarily indicative of the results to be expected for the year ended December 31, 2017 or for any other future annual or interim period. The consolidated balance sheet as of December 31, 2016 included herein was derived from the audited consolidated financial statements as of that date. These interim condensed consolidated financial statements should be read in conjunction with the Company's audited consolidated financial statements included elsewhere in this prospectus.

Unaudited Pro Forma Information

Immediately prior to the completion of this offering, all outstanding shares of convertible preferred stock will convert into common stock. Unaudited pro forma balance sheet information as of

Denali Therapeutics Inc.
Notes to Unaudited Interim Condensed Consolidated Financial Statements

September 30, 2017 assumes the conversion of all outstanding convertible preferred stock into shares of common stock. The shares of common stock issuable and the proceeds expected to be received in the initial public offering are excluded from such pro forma financial information.

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 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 consolidated financial position and results of operations.

Need for Additional Capital

Since inception, the Company has incurred net losses and negative cash flows from operations. During the nine months ended September 30, 2017, the Company incurred a net loss of $65.3 million and used $58.3 million of cash in operations. At September 30, 2017, the Company had an accumulated deficit of $168.8 million and does not expect to experience positive cash flows in the near future. The Company has financed operations to date primarily through the sale and issuance of convertible preferred stock. Management expects to incur additional operating losses in the future as the Company continues the development of, and seeks regulatory approvals for, its product candidates, and begins to commercialize any approved products and recognizes the need to raise additional capital to fully implement its business plan. The Company intends to raise such capital through public and private equity offerings, debt financings, strategic partnerships and alliances and licensing arrangements. The Company had $190.8 million of cash, cash equivalents and marketable securities at September 30, 2017. Based on the Company's business plans, management believes that this is sufficient to meet its obligations for at least the next twelve months from the issuance date of these condensed consolidated financial statements.

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.

Fair Value of Financial Instruments

ASC Topic 820, Fair Value Measurement ("ASC 820"), establishes a fair value hierarchy for instruments measured at fair value that distinguishes between assumptions based on market data (observable inputs) and the Company's own assumptions (unobservable inputs). Observable inputs are inputs that market participants would use in pricing the asset or liability based on market data obtained from sources independent of the Company. Unobservable inputs are inputs that reflect the Company's assumptions about the inputs that market participants would use in pricing the asset or liability, and are developed based on the best information available in the circumstances.

ASC 820 identifies fair value as the exchange price, or exit price, representing the amount that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market

participants. As a basis for considering market participant assumptions in fair value measurements, ASC 820 establishes a three-tier fair value hierarchy that distinguishes between the following:

Level 1 – inputs are quoted prices (unadjusted) in active markets for identical assets or liabilities.

Level 2 – inputs are inputs other than quoted prices included within Level 1 that are observable for the asset or liability, either directly or indirectly.

Level 3 – inputs are unobservable inputs that reflect the Company's own assumptions about the assumptions market participants would use in pricing the asset or liability. Financial assets and liabilities are classified in their entirety based on the lowest level of input that is significant to the fair value measurement.

To the extent that the valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

The carrying amounts reflected in the consolidated balance sheets for cash and cash equivalents, prepaid expenses and other current assets, accounts payable and accrued liabilities approximate their fair values, due to their short-term nature.

Cash and Cash Equivalents

The Company considers all highly liquid investments with original maturities of 90 days or less at the date of purchase to be cash and cash equivalents. Cash equivalents, which consist primarily of highly liquid investments with maturities of three months or less when purchased, are stated at fair value.

Marketable Securities

The Company generally invests its excess cash in money market funds and investment grade short to intermediate-term fixed income securities. Such investments are included in cash and cash equivalents, short-term marketable securities, or long-term marketable securities on the balance sheets, are considered available-for-sale, and reported at fair value with unrealized gains and losses included as a component of stockholders' deficit. The amortized cost of debt securities is adjusted for amortization of premiums and accretion of discounts to maturity, which is included in interest income, net on the consolidated statements of operations. Realized gains and losses and declines in value judged to be other-than-temporary, if any, on marketable securities are included in interest income, net. The cost of securities sold is determined using specific identification.

The Company periodically evaluates whether declines in fair values of its marketable securities below their book value are other-than-temporary. This evaluation consists of several qualitative and quantitative factors regarding the severity and duration of the unrealized loss as well as the Company's ability and intent to hold the marketable security until a forecasted recovery occurs. Additionally, the Company assesses whether it has plans to sell the security or it is more likely than not it will be required to sell any marketable securities before recovery of its amortized cost basis. Factors considered include quoted market prices, recent financial results and operating trends, implied values from any recent transactions or offers of investee securities, credit quality of debt instrument issuers, other publicly available information that may affect the value of the marketable security, duration and severity of the decline in value, and our strategy and intentions for holding the marketable security.

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Restricted Cash

The Company's restricted cash consists of restricted cash in connection with the building leases for the Company's former and current headquarters. The current portion is classified within prepaid expenses and other current assets and the non-current portion within other non-current assets on the accompanying consolidated balance sheets.

Deferred IPO Costs

Deferred IPO costs of $1.2 million are capitalized and included within other non-current assets on the condensed consolidated balance sheet as of September 30, 2017. There were no deferred IPO costs as of December 31, 2016. The deferred IPO costs will be offset against proceeds from the IPO upon the consummation of the IPO. In the event the IPO is terminated, all capitalized deferred IPO costs will be expensed.

Research and Development Expenses

Research and development costs are expensed as incurred. Research and development costs consist of salaries and other personnel related expenses, including associated stock–based compensation, consulting fees, lab supplies, and facility costs, as well as fees paid to other entities that conduct certain research, development and manufacturing activities on behalf of the Company.

Nonrefundable advance payments for goods and services that will be used or rendered in future research and development activities are deferred and recognized as expense in the period in which the related goods are delivered or services are performed.

The Company has acquired and may continue to acquire the rights to develop and commercialize new product candidates from third parties. The upfront payments to acquire license, product or rights, as well as any future milestone payments, are immediately recognized as research and development expense provided that there is no alternative future use of the rights in other research and development projects.

Stock-Based Compensation

The Company measures employee and director stock-based compensation expense for all stock-based awards at the grant date based on the fair value measurement of the award. The expense is recorded on a straight-line basis over the requisite service period, which is generally the vesting period, for the entire award. Expense is adjusted for actual forfeitures of unvested awards as they occur. The Company calculates the fair value measurement of stock options using the Black-Scholes valuation model.

The Company granted restricted stock awards that vest in conjunction with certain performance conditions to certain key employees and directors. At each reporting date, the Company is required to evaluate whether achievement of the performance conditions is probable. Compensation expense is recorded over the appropriate service period based upon the Company's assessment of accomplishing each performance provision.

The Company accounts for stock options issued to non-employees in accordance with the provisions of ASC 505-50, Equity-Based Payments to Non-employees, which requires valuing the stock options on their grant date and remeasuring such stock options at the current fair value at the end of each reporting period until they vest.

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Comprehensive Loss

Comprehensive loss includes net loss and certain changes in stockholders' deficit that are excluded from net loss, primarily unrealized losses on the Company's marketable securities.

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.

Unaudited Pro Forma Net Loss per Share

Pro forma basic and diluted net loss per share has been computed to give effect to the conversion of all outstanding convertible preferred stock into shares of common stock. Pro forma basic and diluted net loss per share has been computed to give effect to the conversion of all outstanding convertible preferred stock into shares of common stock. The unaudited pro forma net loss per share does not include the shares expected to be sold and related proceeds to be received from the initial public offering. The unaudited pro forma net loss per share for the nine months ended September 30, 2017 was computed using the weighted-average number of shares of common stock outstanding, including the pro forma effect of the conversion of all outstanding shares of convertible preferred stock into shares of common stock, as if such conversion had occurred at the beginning of the period, or their issuance dates if later.

Recent Accounting Pronouncements

In May 2014, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update ("ASU") No. 2014–09 ("ASU 2014-09"), Revenue from Contracts with Customers (Topic 606), and further updated through ASU 2016-12 ("ASU 2016-12"), which amends the existing accounting standards for revenue recognition. ASU 2014–09 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 guidance is effective for annual reporting periods, and interim periods within those years, beginning after December 15, 2017, for public entities and no later than for annual reporting periods beginning after December 15, 2018, for non–public entities. Early adoption is not permitted. The new revenue standard may be applied retrospectively to each prior period presented or retrospectively with the cumulative effect recognized as of the date of adoption. While the Company continues to assess all potential impacts under ASU 2014-09, it does not believe adopting the new revenue standard will have a material impact on its consolidated financial statements as the Company is not yet generating revenues.

In February 2016, the FASB issued ASU No. 2016-02 ("ASU 2016-02"), Leases (Topic 842), which supersedes the guidance in former ASC 840, Leases. 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. The ASU 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 currently evaluating the impact the adoption of ASU 2016-02 will have on the Company's financial position and results of operations. Management expects that the adoption of this standard will result in the recognition of an asset for the right to use the 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 does not expect a material change to the consolidated statement of operations.

In November 2016, the FASB issued ASU 2016-18, Statement of Cash Flows (Topic 230): Restricted Cash. The purpose of Update No. 2016-18 is to clarify guidance and presentation related to 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. The update is effective for fiscal years beginning after December 15, 2017, including interim reporting periods within those fiscal years. Early adoption is permitted. The Company is currently evaluating the impact of adopting this standard on the consolidated financial statements and disclosures, but does not expect it to be material.

In May 2017, the FASB issued ASU 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. It is effective for annual and interim periods beginning after December 15, 2017. Early adoption is permitted. The Company is currently evaluating the impact of adopting this standard on the consolidated financial statements and disclosures, but does not expect it to have a significant impact.

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2. Fair Value Measurements

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

	December 31, 2016			
	Level 1	Level 2	Level 3	Total
Assets:				
Money market funds	$28,705	$ —	$ —	$ 28,705
Short-term:				
U.S. government treasuries	22,268	—	—	22,268
U.S. government agency securities	—	70,787	—	70,787
Corporate debt securities	—	38,941	—	38,941
Commercial paper	—	6,482	—	6,482
Long-term:				
U.S. government treasuries	4,989	—	—	4,989
U.S. government agency securities	—	52,868	—	52,868
Corporate debt securities	—	14,723	—	14,723
Total marketable securities	27,257	183,801	—	211,058
Total fair value measurements	**$55,962**	**$183,801**	**$ —**	**$239,763**

	September 30, 2017			
	Level 1	Level 2	Level 3	Total
Assets:				
Money market funds	$30,399	$ —	$ —	$ 30,399
Short-term:				
U.S. government treasuries	14,710	—	—	14,710
U.S. government agency securities	—	99,972	—	99,972
Corporate debt securities	—	34,850	—	34,850
Long-term:				
U.S. government agency securities	—	4,975	—	4,975
Total marketable securities	14,710	139,797	—	154,507
Total fair value measurements	**$45,109**	**$139,797**	**$ —**	**$184,906**

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 nine months ended September 30, 2017.

3. Marketable Securities

All marketable securities were considered available-for-sale at December 31, 2016 and September 30, 2017. The amortized cost, gross unrealized holding gains or losses, and fair value of

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the Company's marketable securities by major security type at each balance sheet date are summarized in the tables below (in thousands):

	December 31, 2016			
	Amortized Cost	Unrealized Holding Gains	Unrealized Holding Losses	Aggregate Fair Value
Short-term marketable securities:				
U.S. government treasuries	$ 22,277	$ —	$ (9)	$ 22,268
U.S. government agency securities	70,835	—	(48)	70,787
Corporate debt securities	39,037	—	(96)	38,941
Commercial paper	6,482	—	—	6,482
Total short-term marketable securities	138,631	—	(153)	138,478
Long-term marketable securities:				
U.S. government treasuries	4,996	1	(8)	4,989
U.S. government agency securities	53,005	—	(137)	52,868
Corporate debt securities	14,799	—	(76)	14,723
Total long-term marketable securities	72,800	1	(221)	72,580
Total	**$ 211,431**	**$ 1**	**$ (374)**	**$ 211,058**

	September 30, 2017			
	Amortized Cost	Unrealized Holding Gains	Unrealized Holding Losses	Aggregate Fair Value
Short-term marketable securities:				
U.S. government treasuries	$ 14,726	$ —	$ (16)	$ 14,710
U.S. government agency securities	100,118	—	(146)	99,972
Corporate debt securities	34,900	—	(50)	34,850
Total short-term marketable securities	149,744	—	(212)	149,532
Long-term marketable securities:				
U.S. government agency securities	5,000	—	(25)	4,975
Total long-term marketable securities	5,000	—	(25)	4,975
Total	**$ 154,744**	**$ —**	**$ (237)**	**$ 154,507**

As of December 31, 2016 and September 30, 2017, some of the Company's marketable securities were in an unrealized loss position. At each date, the Company determined that it did have 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 in the year ended December 31, 2016 or the nine months ended September 30, 2017. All marketable securities with unrealized losses as of 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 short-term marketable securities have an effective maturity date of less than one year, and all of the Company's long-term marketable securities have an effective maturity of less than two years.

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4. Acquisition

In June 2015, the Company acquired Incro Pharmaceuticals Corporation ("Incro"), a preclinical private biotechnology company incorporated in Delaware. The primary asset purchased in the acquisition was an in-process research and development license agreement which would allow the Company to further its RIPK1 research program. The Company concluded that the assets acquired and liabilities assumed did not meet the accounting definition of a business as a limited number of inputs were acquired but no processes were acquired, and the licensed technology had not achieved technological feasibility. As such, the acquisition was accounted for as an asset purchase and the Company recorded the purchase price as $1.5 million in research and development expense in the accompanying statement of operations and comprehensive loss in the year ended December 31, 2015.

As purchase consideration the Company issued an aggregate of 472,942 shares of common stock, valued at $0.6 million on the transaction date, to the former Incro stockholders, and recognized within additional paid-in capital an obligation to issue an additional 27,054 shares of common stock, valued at $32,466 to one former Incro stockholder. The deemed fair value (see Note 8) of the Company's common stock was $1.20 per common share as of the date of the transaction. In addition to the issuance of this equity, the Company assumed liabilities of $0.9 million.

The Company also agreed to issue an additional 945,880 shares of common stock to the former Incro stockholders, and to recognize an obligation to issue 54,110 shares of common stock to one former Incro shareholder ("Milestone Shares"), upon acceptance of an investigational new drug ("IND") application by the U.S. FDA or an equivalent in the EU, Canada, Australia, or New Zealand within six years of the date of the acquisition. Of these shares, 350,000 shares of common stock ("Indemnification Shares") were to be held in escrow by Denali, and would be released to former stockholders of Incro within 30 days of the later of (i) expiration of 18 months after the closing; and (ii) the date the Milestone Shares vest as noted above. The number of Indemnification Shares to be released to Incro's stockholders were to be reduced to the extent of breaches of standard representations by Incro's stockholders. 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.

In August 2016, the Company filed a Clinical Trial Application ("CTA") in Europe to initiate a Phase 1 clinical trial. Upon acceptance of the CTA in September 2016, the issuance of the Milestone Shares was triggered. The Company issued a total of 595,880 shares of common stock, recognized an obligation to issue 54,110 shares of common stock, and recorded a liability of $1.8 million for the 350,000 Indemnification Shares held in escrow. The Company recognized $5.3 million of research and development expense related to the estimated fair value of these shares of $5.28 per share during the nine months ended September 30, 2016. In December 2016, the 350,000 Indemnification Shares were released and issued and the related liability was extinguished upon the expiration of the 18-month period after the closing of the acquisition.

5. License and Collaboration Agreements

F-star

On August 24, 2016, the Company entered into a License and Collaboration Agreement ("Collaboration Agreement") with F-star Gamma Limited ("F-star Gamma"), f-star Biotechnologische Forschungs-und Entwicklungsges m.b.H and F-star Biotechnology Limited (collectively, "F-star"). The goal of the collaboration is the development of certain constant Fc-domains of an antibody with

non-native antigen binding activity ("Fcabs"), to enhance delivery of therapeutics across the blood-brain barrier ("BBB") into the brain. The collaboration leverages F-star's modular antibody technology and the Company's expertise in the development of therapies for neurodegenerative diseases.

Under the terms of the Collaboration Agreement, the Company can nominate up to three Fcab targets ("Accepted Fcab Targets"), within the first three years of the date of the Collaboration Agreement; and the Company has selected transferrin receptor ("TfR") as the first Accepted Fcab Target. With respect to each Accepted Fcab Target, the Company can nominate up to eight Fab targets ("Accepted Fab Targets"), which are targets bound by the variable domains of an antibody or other therapeutic modalities ("Fabs"). For each accepted Fcab target, the Company is obligated to use commercially reasonable efforts during the research term to perform development activities in accordance with certain specified development plans. Under the terms of the Collaboration Agreement, the Company received non-exclusive licenses under certain intellectual property to conduct technology development to discover and develop Fcabs. The Company is obligated to assign to F-star certain patents and know-how that the Company generates under the Collaboration Agreement related to F-star's platform technology or certain Fcabs identified solely by F-star and the Company received a non-exclusive license under certain of F-star Biotechnology's platform patents and know-how to develop and commercialize products in connection with the delivery of therapeutics across the BBB, subject to certain specified restrictions. F-star retains the right to use its intellectual property, including any intellectual property that the Company and F-star jointly own pursuant to the terms of the Collaboration Agreement, outside the scope of the licenses granted to the Company.

Under the terms of the Collaboration Agreement, the Company paid F-star Gamma an upfront fee of $5.5 million, which includes selection of the first Accepted Fcab Target. The Company is obligated to pay a one-time fixed fee in the low single-digit millions for each additional Accepted Fcab Target the Company selects, technical milestone payments for each Accepted Fcab Target, up to a maximum of $15.0 million in the aggregate for all Accepted Fcab Targets, and, at specified times, monthly exclusivity fees for Accepted Fcab Targets and Accepted Fab Targets, which may be eliminated in certain circumstances. The Company is also responsible for certain research costs incurred by F-star 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.

Either party may terminate the agreement if the other party materially breaches the agreement, subject to specified notice and cure provisions, or for the other party's bankruptcy or insolvency. In addition, F-star Gamma may terminate the agreement if the Company challenges any of the patent rights licensed to it by F-star. The Company is able to terminate the agreement for convenience, either in its entirety or on an Accepted Fcab Target-by-Accepted Fcab Target basis or an Accepted Fab Target-by-Accepted Fab Target basis, on 90 days' prior written notice to F-star. Unless earlier terminated, the agreement with F-star will remain in effect until all royalty and milestone payment obligations to F-star Gamma expire.

In connection with the entry into the 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"). The Company must elect whether to exercise its buy-out option before the earlier of (i) dosing of the fifth patient dosed in the first Phase 1 trial of an antibody that binds to an Accepted Fab Target and an Accepted Fcab Target, (ii) the fourth anniversary of the first delivery by F-star of an Fcab meeting certain delivery criteria, and (iii) five and one half years after the delivery by the Company of a notice that it is progressing an Fcab identified from the Company's library that binds to

an Accepted Fcab Target. If the Company exercises this buy-out option, it will be obligated to make initial exercise payments ranging from $18.0 million to $50.0 million in the aggregate, plus the estimated net cash held by F-star Gamma at the time of such exercise. In addition, it will be required to make certain contingent payments upon the achievement of certain preclinical, clinical, regulatory and commercial milestones, up to a maximum amount of $447.0 million in the aggregate. The amount of the initial exercise and contingent payments varies based on whether F-star delivers an Fcab that meets pre-defined criteria, whether the Fcab has been identified solely by the Company or solely by F-star or jointly by the Company and F-star and the timing of the Company's exercise of the buy-out option. Following exercise of the buy-out option, the Company will not be required to make any further milestone or royalty payments under the Collaboration Agreement. If the Company exercises the buy-out option, then f-star Biotechnologische Forschungs-und Entwicklungsges m.b.H and F-star Biotechnology continue to be prohibited from developing, commercializing and manufacturing any antibody or other molecule that incorporates any Selected Fcab, or any Selected Fcab as a standalone product, and from authorizing any third party to take any such action. If the Company does not exercise its option to acquire F-star Gamma prior to the expiration of the buy-out option period, then, from the lapse of the buy-out option period until the Company's rights with respect to an Accepted Fab Target expire or terminate, F-star is prohibited from developing, commercializing and manufacturing any antibody or other molecule that contains both a Selected Fcab and a Fab that specifically binds to the relevant Accepted Fab Target.

If the Company does not exercise the buy-out option, then with respect to each Accepted Fab Target, the Company has the right to obtain from F-star an exclusive, worldwide license to certain intellectual property to develop and commercialize licensed products that contain (i) a Fab that specifically binds to such Accepted Fab Target and (ii) an Fcab that the Company or F-star identifies, either solely or jointly, and that specifically binds to an Accepted Fcab Target, for up to eight Accepted Fab Targets per each Accepted Fcab Target. Each time the Company exercises such license option, it will be obligated to pay F-star Gamma (i) a one-time fixed fee in the low single-digit millions, (ii) milestone payments upon the achievement of certain clinical development and commercial milestones, up to a maximum of $362.5 million in the aggregate; (iii) additional sales-based milestones if net sales of licensed products achieve certain specified levels, up to a maximum amount payable to F-star of $650.0 million in the aggregate and (iv) low-to-mid single-digit percentage royalties on net sales of licensed products. Such amounts may be reduced by a specified percentage depending on the origin of the Fcab incorporated in the applicable licensed product and whether F-star delivers to the Company an Fcab that meets pre-defined criteria. The Company has the right to credit a certain amount of royalty payments that it pays to third parties with respect to certain licensed products against the Company's royalty obligation to F-star Gamma, 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) the expiration of the last valid claim of a licensed patent covering such licensed product in such country, (b) the expiration of regulatory exclusivity for such licensed product in such country and (c) the twelfth anniversary of the first commercial sale of such licensed product in such country.

The Company recognized the upfront option fee of $0.5 million within other non-current assets recorded at cost. This asset will be assessed for potential impairment on an ongoing basis. No impairment charge was recognized during the nine months ended September 30, 2016 or 2017.

The Company determined that F-star Gamma is and continues to be a variable interest entity and that the Company holds a variable interest in F-star Gamma's intellectual property assets and the related potential future product candidates these assets may produce through the Collaboration

Agreement and the Option Agreement. However, the Company concluded that its governance role in the collaboration, which is specified by the terms of a joint steering committee, does not provide the Company the power to direct the activities of F-star Gamma that most significantly impact F-star Gamma's economic performance. Based on this conclusion, the Company is not considered to be the primary beneficiary of F-star Gamma; and therefore F-star Gamma is not subject to consolidation by the Company.

The Company recognized $0.8 million of research and development expense related to the funding of F-star Gamma research costs during the nine months ended September 30, 2017. No such expense was recognized in the nine months ended September 30, 2016.

The $0.5 million other non-current asset is the only asset or liability recorded in the Company's interim condensed consolidated balance sheets that relates to the Company's variable interest in F-star Gamma at December 30, 2016 and September 30, 2017. The upfront payments of $0.5 million and $5.5 million, along with 1) the obligation to fund certain future research costs, 2) any future Fcab selection fee, technical milestone payments or monthly exclusivity fees and 3) any future license fees or pre-commercial milestone payments represent the Company's maximum exposure to loss under the arrangements with F-star. The ultimate expense that the Company incurs under the arrangements with F-Star cannot be quantified at this time as the amount will vary based on the timing and outcome of future research activities.

Genentech

On June 17, 2016, the Company entered into an Exclusive License Agreement with Genentech, Inc. ("Genentech"). The agreement gives the Company access to Genentech's preclinical stage LRRK2 small molecule program, which can be used to enhance and further progress the Company's in-house LRRK2 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 are included within research and development expense for the nine months ended September 30, 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.

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 payment 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 included in research and development expense in the nine months ended September 30, 2017.

6. 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 ("Headquarters Lease"). The Headquarters Lease commenced on August 1, 2016 with a lease term of eight years. The Company has an option to extend the lease term for a period of five 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 original expiration of the lease term. The Headquarters Lease provides for monthly base rent amounts escalating over the term of the lease. In addition, the Headquarters Lease provides both a tenant improvement allowance ("TIA") of up to $7.4 million, of which $1.9 million will 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 results in an increase of base rent of $0.4 million per year.

The total $7.4 million TIA has been recorded as leasehold improvements and deferred rent liability on the consolidated balance sheet. 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 lease term. Under the terms of the Headquarters Lease, the Company was required to pay a security deposit of $0.5 million, which is recorded as other non-current assets in the accompanying consolidated balance sheets.

In May 2015, the Company entered into a non-cancelable operating lease for office and research and development space in South San Francisco that expires in December 2017 (the "First Lease"). The

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First Lease provides for 9,855 of rentable square feet at a base rent that increases annually. Under the terms of the First Lease, the Company was required to pay a security deposit of $0.1 million, which is recorded as prepaid expenses other current assets in the accompanying consolidated balance sheets.

On July 22, 2016, the Company entered into a sublease agreement with a third party for the entirety of the remaining term of the First Lease. The sublease commenced on August 22, 2016. The Company received sublease payments totaling $42,000 and $0.3 million in the nine months ended September 30, 2016 and 2017, respectively. The Company expects to receive future minimum payments from this sublease of $0.1 million in the remainder of 2017, which will be recognized as an offset to rent expense.

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, 2017, the future minimum lease payments under non-cancelable operating leases are as follows (in thousands):

Year Ended December 31:	
2017 (three months)	$ 729
2018	2,586
2019	2,664
2020	2,745
2021	2,829
2022 and later	7,704
	$19,257

Rent expense for the nine months ended September 30, 2016 and 2017 was $0.5 million and $1.6 million, respectively.

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 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 DMSA will expire on September 6, 2022. As of September 30, 2017, the Company had not incurred any amounts or made any purchase commitments under the DMSA. In October 2017, the Company executed the first purchase order of up to $0.7 million, the activities under which will commence prior to the end of 2017.

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7. Convertible Preferred Stock and Stockholders' Deficit

Convertible Preferred Stock

At December 31, 2016, convertible preferred stock consisted of the following (in thousands, except share and per share amounts):

	Shares Authorized	Shares Issued and Outstanding	Issuance Price per Share	Carrying Value	Liquidation Preference
Series A-1	46,114,433	46,114,423	$ 4.00	$183,951	$198,264
Series A-2	4,361,533	4,361,527	8.00	34,885	36,483
Series B-1	8,125,000	8,124,365	16.00	129,837	135,324
Series B-2	4,687,500	—	—	—	—
	63,288,466	58,600,315		$348,673	$370,071

At September 30, 2017, convertible preferred stock consisted of the following (in thousands, except share and per share amounts):

	Shares Authorized	Shares Issued and Outstanding	Issuance Price per Share	Carrying Value	Liquidation Preference
Series A-1	46,114,433	46,114,423	$ 4.00	$183,951	$209,301
Series A-2	4,361,533	4,361,527	8.00	34,885	38,571
Series B-1	8,125,000	8,124,365	16.00	129,837	143,102
Series B-2	4,687,500	—	—	—	—
	63,288,466	58,600,315		$348,673	$390,974

Common Stock

As of September 30, 2017, the Company had reserved shares of common stock for issuance as follows:

Series A-1 convertible preferred stock outstanding	46,114,433
Series A-2 convertible preferred stock outstanding	4,361,533
Series B-1 convertible preferred stock outstanding	8,125,000
Series B-2 convertible preferred stock outstanding	4,687,500
Options issued and outstanding	6,179,687
Restricted shares subject to future vesting	2,701,059
Early exercised common stock subject to future vesting	416,669
Options available for future grant	312,456
Shares to be issued under Incro acquisition agreement	81,164
Total	72,979,501

8. Stock Incentive Plan

2015 Stock Incentive Plan

As of September 30, 2017, there were 312,456 shares available for the Company to grant under the 2015 Stock Incentive Plan (the "2015 Plan").

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Stock Option Activity

The following table summarizes option award activity under 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, 2016	5,374,014	$ 1.77	9.03	$ 18,873
Options granted	1,622,629	6.48		
Options exercised	(695,192)	1.41		
Options forfeited	(121,764)	0.95		
Balance at September 30, 2017	6,179,687	$ 3.06	8.61	$ 53,006
Options vested and expected to vest at September 30, 2017	4,434,941	$ 4.00	8.89	$ 33,884
Options exercisable at September 30, 2017	854,786	$ 3.12	8.71	$ 7,282

The aggregate intrinsic values of options outstanding, exercisable, vested and expected to vest were calculated as the difference between the exercise price of the options and the estimated fair value of the Company's common stock, as determined by the Board of Directors, as of September 30, 2017.

During the nine months ended September 30, 2016 and 2017, the estimated weighted-average grant-date fair value of the options vested was $0.99 and $2.08 per share, respectively, and the estimated weighted-average grant-date fair value of common stock underlying options granted was $2.12 and $4.84 per share, respectively.

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

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

	Nine Months Ended September 30,	
	2016	2017
Expected term (in years)	6.00-6.08	6.08
Volatility	91.2%-92.2%	86.8%-91.3%
Risk-free interest rate	1.2%-1.5%	1.8%-2.3%
Dividend yield	—	—

Denali Therapeutics Inc.
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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. The estimated fair value of the stock options granted is calculated at each reporting date using the Black-Scholes option-pricing model with the following assumptions:

	Nine Months Ended September 30,	
	2016	2017
Expected term (in years)	8.75-9.90	7.75-9.45
Volatility	93.9%-98.3%	86.8%-98.0%
Risk-free interest rate	1.5%-1.6%	2.2%-2.4%
Dividend yield	—	—

Restricted Stock Activity

The following table summarizes restricted stock activity:

	Shares	Weighted-Average Fair Value at Date of Grant per Share
Unvested at December 31, 2016	3,922,638	$ 0.18
Granted	—	—
Vested	(1,221,579)	0.18
Forfeited	—	—
Unvested at September 30, 2017	2,701,059	$ 0.18
Vested and expected to vest – September 30, 2017	2,701,059	$ 0.18

At September 30, 2017, there was $0.4 million of total unrecognized compensation cost related to non-vested restricted stock, all which is expected to be recognized over a remaining weighted-average period of 1.3 years.

Stock-Based Compensation Expense

The Company's results of operations include expenses relating to employee and non-employee stock-based awards and restricted stock awards, as follows (in thousands):

	Nine Months Ended September 30,	
	2016	2017
Research and development	$ 1,600	$ 1,947
General and administrative	660	1,005
Total	$ 2,260	$ 2,952

As of September 30, 2017, total unamortized stock-based compensation expense related to unvested employee and non-employee awards that are expected to vest was $12.5 million and $0.5 million respectively. The weighted-average period over which such stock-based compensation expense will be recognized is approximately 3.1 years.

Denali Therapeutics Inc.
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The Company recorded stock-based compensation expense for options issued to non-employees under the 2015 Plan of $1.0 million and $0.5 million for the nine months ended September 30, 2016 and 2017, respectively.

9. Net Loss and Unaudited Pro Forma 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):

	Nine Months Ended September 30,	
	2016	2017
Numerator:		
Net loss	$ (67,298)	$ (65,298)
Denominator:		
Weighted average common shares outstanding	5,888,385	9,643,686
Net loss per share, basic and diluted	$ (11.43)	$ (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:

	September 30,	
	2016	2017
Series A-1 convertible preferred stock	46,114,423	46,114,423
Series A-2 convertible preferred stock	4,361,527	4,361,527
Series B-1 convertible preferred stock	8,124,365	8,124,365
Options issued and outstanding	4,920,232	6,179,687
Restricted shares subject to future vesting	4,414,322	2,701,059
Early exercised common stock subject to future vesting	671,875	416,669
Shares to be issued under Incro acquisition agreement	81,164	81,164
Total	68,687,908	67,978,894

Pro Forma Net Loss Per Share

The following table sets forth the computation of the Company's unaudited pro forma basic and diluted net loss per share (in thousands, except for share and per share amounts):

	Nine Months Ended September 30, 2017
Net loss	$ (65,298)
Shares used in computing net loss per share, basic and diluted	9,643,686
Pro forma adjustment to reflect assumed conversion of preferred stock	58,600,342
Shares used to compute pro forma net loss per share, basic and diluted	68,244,028
Pro forma net loss per share, basic and diluted	$ (0.96)

Denali Therapeutics Inc.
Notes to Unaudited Interim Condensed Consolidated Financial Statements

10. Subsequent event

In November 2017, the Company sold 1,764,705 shares of Series B-2 convertible preferred stock at a price of $17.00 per share for net proceeds of $29.9 million. In connection with this financing, the Company amended and restated its certificate of incorporation to reflect that the holders of preferred stock are entitled to receive dividends, if and when declared by the Board of Directors, at the rate of $0.34 per share per annum, and to establish the Series B-2 original issuance price at $4.25 per share, both subject to adjustment in the event of a stock split, combination, common stock dividend or distribution, reclassification, exchange, substitution, or reorganization. The amendments provided for rights, preferences and privileges for the Series B-2 convertible preferred stock similar to those of the Series A-1, A-2 and B-1 convertible preferred stock.

13,888,888 Shares

Denali Therapeutics Inc.

Common Stock

Goldman Sachs & Co. LLC **Morgan Stanley** **J.P. Morgan**

Evercore ISI