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

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2019

OR

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

For the transition period from __________ to __________

Commission File Number: 001-38311

Denali Therapeutics Inc.
(Exact name of registrant as specified in its charter)

Delaware	**46-3872213**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**

161 Oyster Point Blvd.
South San Francisco, CA, 94080

(Address of principal executive offices and zip code)

(650) 866-8548
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol	Name of each exchange on which registered
Common Stock, par value $0.01 per share	DNLI	The NASDAQ Global Select Market

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Securities Exchange Act. Yes ☐ No ☒

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

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

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405 of this chapter) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☒

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

Large accelerated filer	☒	Accelerated filer	☐
Non-accelerated filer	☐	Smaller reporting company	☐
		Emerging growth company	☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.☐

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

The aggregate market value of the common stock held by non-affiliates of the registrant as of June 28, 2019 (the last business day of the registrant's most recently completed second fiscal quarter) was approximately $715.6 million, based on the closing price of the registrant's common stock, as reported by the NASDAQ Global Select Market on June 28, 2019 of $20.76 per share. Shares of the registrant's common stock held by each executive officer, director and holder of 5% or more of the outstanding common stock have been excluded in that such persons may be deemed to be affiliates. This calculation does not reflect a determination that certain persons are affiliates of the registrant for any other purpose.

The number of outstanding shares of the registrant's common stock as of February 19, 2020 was 105,423,277 par value $0.01 per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE:

Portions of the registrant's Definitive Proxy Statement relating to the registrant's 2019 Annual Meeting of Stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K where indicated. Such Definitive Proxy Statement will be filed with the Securities and Exchange Commission within 120 days after the end of the registrant's 2019 fiscal year ended December 31, 2019.

Denali Therapeutics Inc.
Annual Report on Form 10-K
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PART I

Special Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K contains forward-looking statements. All statements other than statements of historical facts contained in this report, 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 report 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 blood-brain barrier ("BBB") platform technology, programs and biomarkers;
- the extent to which any dosing limitations that we have been subject to and/or may be subject to in the future, may affect the success of our product candidates;
- the impact of preclinical findings on our ability to achieve exposures of our product candidates that allow us to explore a robust pharmacodynamic range of these candidates in humans;
- the expected potential benefits of strategic collaborations with third parties and our ability to attract collaborators with development, regulatory and commercialization expertise;
- the timing or likelihood of regulatory filings and approvals;
- our ability to obtain and maintain regulatory approval of our product candidates, and any related restrictions, limitations and/or warnings in the label of any approved product candidate;
- the scope of protection we are able to establish and maintain for intellectual property rights covering our product candidates and technology;
- the terms and conditions of licenses granted to us and our ability to license 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 and commercialized;
- the success of competing products or platform technologies that are or may become available;
- our ability to attract and retain key managerial, scientific and medical personnel;
- the accuracy of our estimates regarding expenses, future revenue, capital requirements and needs for additional financing; and
- our financial performance.

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 report and are subject to a number of risks, uncertainties and assumptions described in the section titled “Risk Factors” and elsewhere in this report. 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 undertake no obligation to update publicly any forward-looking statements for any reason after the date of this Annual Report on Form 10-K to conform these statements to actual results or to changes in expectations.

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 report, 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.

This report 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 report 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.

ITEM 1. 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 neurodegenerative diseases. 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.

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

Genetic Pathway Potential - We select our therapeutic targets and disease pathways based on studies that link human genetic variation to the risk of developing a neurodegenerative disease. These studies identify 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 ("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.

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 have a focused yet diversified portfolio with fifteen programs.

To further increase the probability of success of our programs, we make parallel investments in lead and back-up development candidates, and plan to advance only those candidates to the later stages of clinical development that show strong preclinical and early clinical data. We 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. We maintain a high bar to move our product candidates through development and quickly terminate molecules and programs based on data that do not meet our rigorous discovery and development standards.

Collaborations and partnering are central components of our strategy to build and develop our portfolio of product candidates. We have arrangements with biopharmaceutical companies, technology companies, academic institutions, foundations, and patient-focused data companies. Notable active arrangements we have include those with Takeda Pharmaceutical Company Limited ("Takeda"), Genzyme Corporation, a wholly owned subsidiary of Sanofi S.A. ("Sanofi"), Genentech, Inc., F-star, Sirion, Harvard University, the Michael J. Fox Foundation, and Centogene, amongst others. Through these arrangements, we are able to gain access to new product candidates, deepen our scientific understanding of certain areas of biology, identify potential patients for our clinical trials and thereby accelerate and increase the probability of success of the development of our programs. We believe that being an active participant in the scientific community and accessing external innovation is important to our success and we plan to remain active in 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, deep scientific expertise in neurodegeneration and BBB biology, established research and development capabilities and ability to execute development programs with speed and scientific rigor.

We have retained significant development and commercialization rights to all of our programs, including the programs partnered with Takeda, as well as with Sanofi for central nervous system ("CNS") indications, where we share responsibility for clinical development and share commercialization rights in the US and China.

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, 5.8 million people suffer from Alzheimer's disease, as many as one million people suffer from Parkinson's disease, and more than 16,000 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 enormous. The direct costs of caring for individuals with Alzheimer's disease and other dementias in the United States were an estimated $290 billion in 2019. By 2050, these costs could rise to $1.1 trillion, 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.

Our target indications include diseases with large patient populations, such as Alzheimer's disease and Parkinson's disease, as well as orphan indications, such as mucopolysaccharidosis type II ("MPS II", or "Hunter syndrome"), and amyotrophic lateral sclerosis ("ALS").

Degenogene Biology

Since 2007, the number of genetic associations discovered in neurodegenerative diseases has grown rapidly. Degenogenes identify important disease pathways that, when dysregulated, increase the risk of developing neurodegenerative disease, and provide a strong scientific foundation for prioritizing drug development programs. We currently focus on programs that seek to modulate three key disease 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 ("LSDs"). Degenogenes linked to lysosomal function include leucine-rich repeat kinase 2 ("LRRK2"), progranulin ("PGRN"), alpha-synuclein ("aSyn"), and lysosomal enzymes, including iduronate 2-sulfatase ("IDS"), Sulfamidase ("SGSH"), and glucocerebrosidase ("GBA").

Glial Biology: Degenogenes implicate immune dysfunction in the brains of patients with Alzheimer's disease and other neurodegenerative diseases. These degenogenes 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, receptor interacting serine/threonine protein kinase 1 ("RIPK1"), a kinase downstream of the TNF receptor pathway, is overactive in inflamed microglia and several other cells in the brain.

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Cellular Homeostasis: The brain is particularly susceptible to defects in lipid, protein or RNA homeostasis. Mutations in several ALS / Frontotemporal Dementia ("FTD") degenogenes alter RNA homeostasis and increase cellular stress. EIF2B is an essential regulator of cellular stress, and modulators of EIF2B activity have been shown to be beneficial in numerous in vitro and in vivo models of neurodegenerative disease. Other degenogenes linked to cellular homeostasis include amyloid precursor protein ("APP"), Tau and Apolipoprotein E.

BBB Platform Technology

Our Transport Vehicle ("TV") technology enables several classes of biotherapeutics to more effectively cross the BBB, including enzymes, antibodies, proteins and oligonucleotides. 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 1).

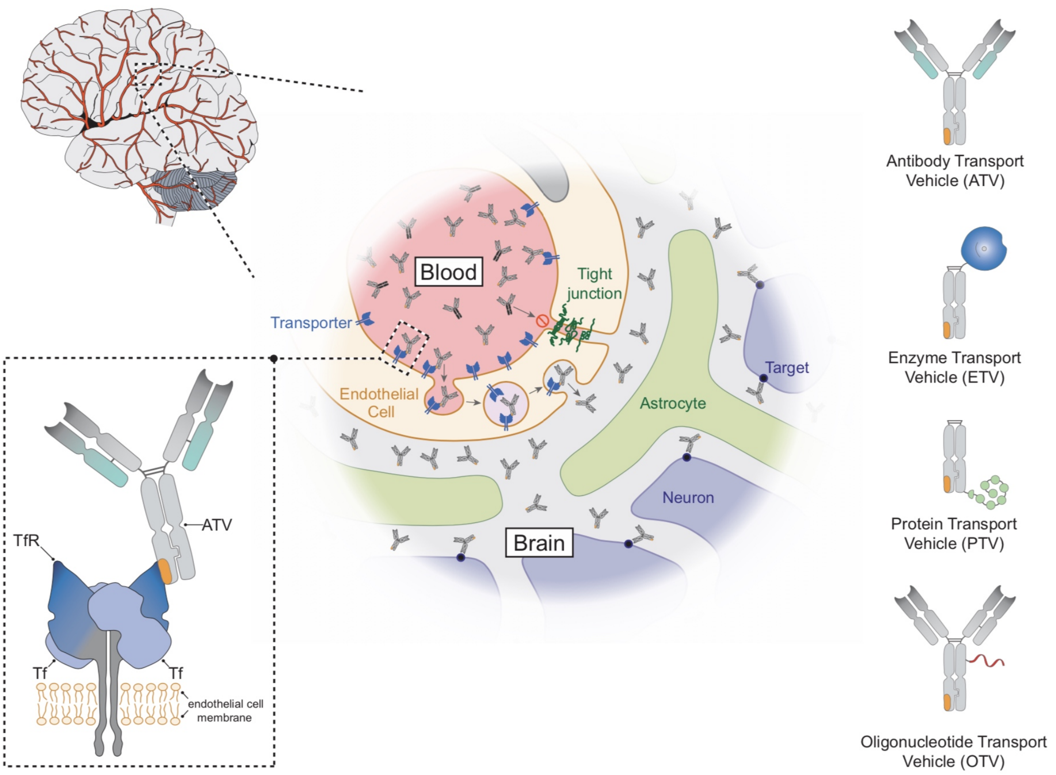

Figure 1: Engineering brain delivery. Schematic of the TV technologies, designed to cross the BBB through receptor-mediated transcytosis, leveraging endogenous receptors expressed on endothelial cells in the vasculature of the brain.

The platform has demonstrated proof of concept safety and pharmacokinetic/pharmacodynamic data in mouse and nonhuman primate models, including a robust and sustained pharmacodynamic effect in the brain after intravenous ("IV") dosing of a TV-enabled antibody, while a standard antibody had minimal pharmacodynamic effect, and robust and sustained efficacy in the brain in a mouse model of Hunter syndrome after IV dosing of a TV-enabled IDS enzyme, while a standard recombinant IDS enzyme had only minimal effect. The improvement in brain exposure may enable TV-enabled product candidates to achieve therapeutically relevant concentrations in the brain after systemic administration, making them potentially superior to traditional antibody and enzyme therapeutics in targeting neurodegenerative diseases. Our TV technology is differentiated from other BBB technologies through its engineering approach, which may provide superior stability, safety, and higher exposure of drug candidates in the brain.

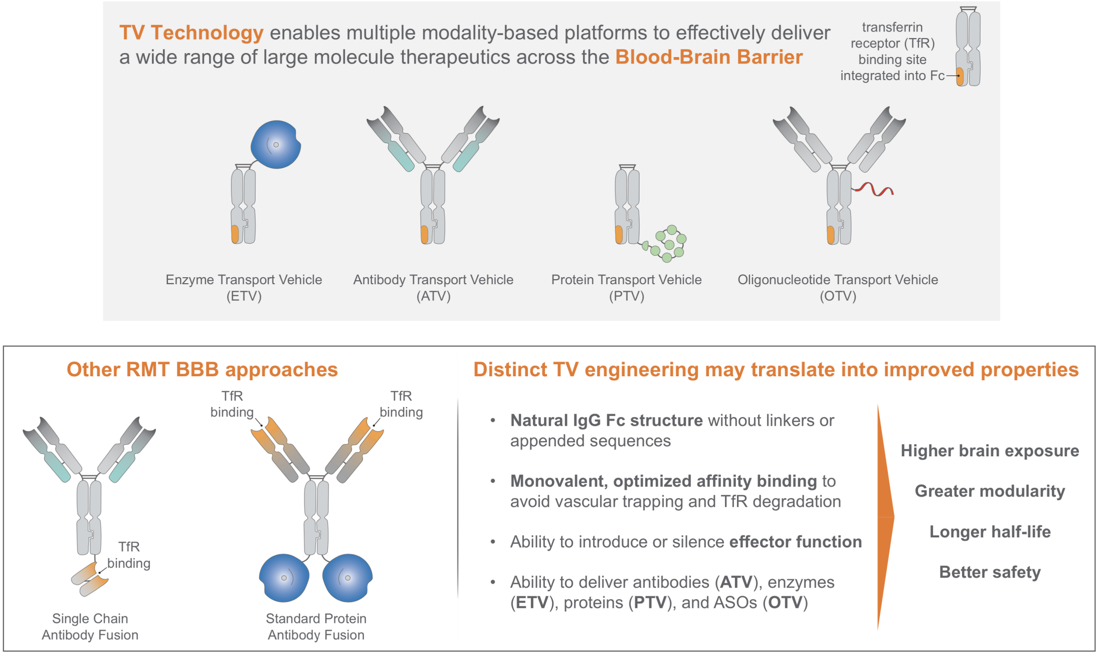

Figure 2: Transport Vehicle technology is highly differentiated

Our pipeline includes nine programs that are based on our TV technology, including the most advanced program ETV:IDS (DNL310) for which we expect to initiate a Phase 1/2 study in patients with Hunter syndrome in the first half of 2020 and obtain human proof of concept data by the end of 2020. Leveraging the modularity of the TV technology, we believe we can expand our portfolio with several new programs in the future.

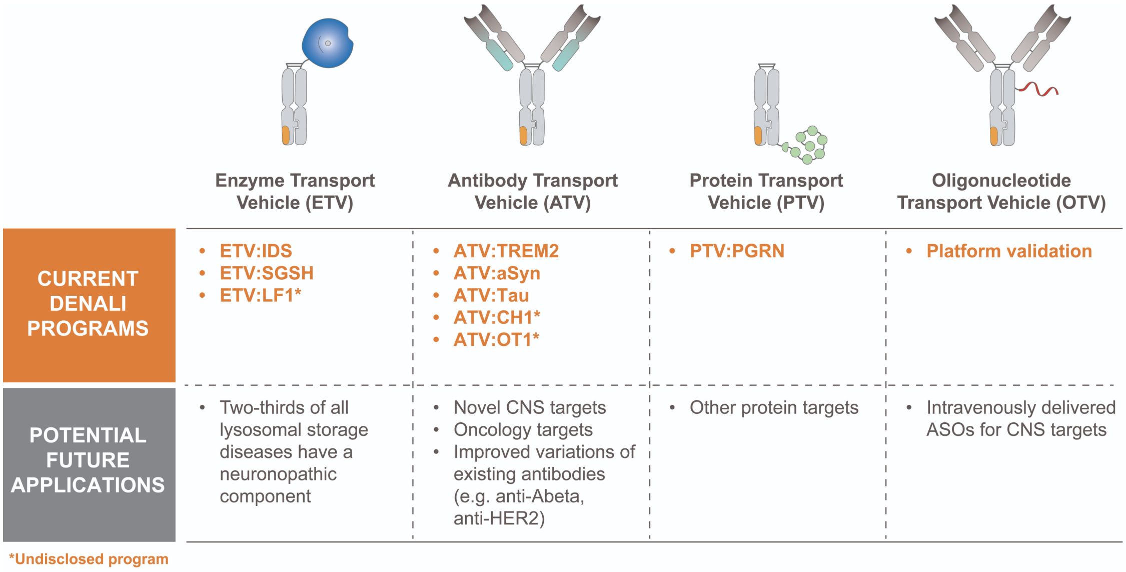

Figure 3: Transport Vehicle technology provides opportunities for platform expansion

Biomarkers

As part of our strategy, we identify and validate 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. 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

The following table summarizes key information about our programs and pipeline:

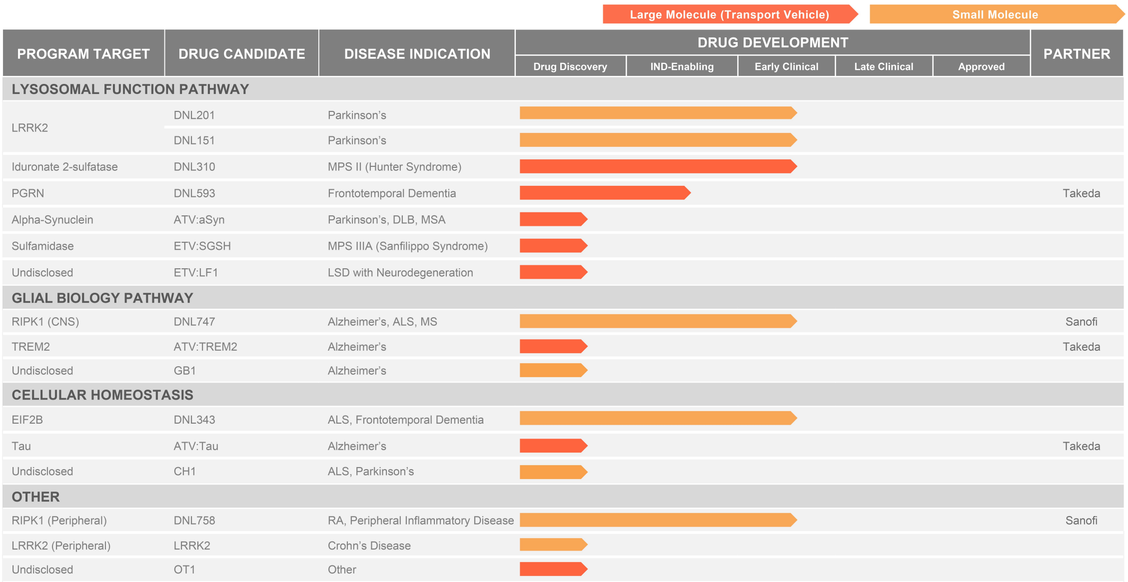

Figure 4: Denali's Current pipeline

We are developing a broad portfolio of targeted therapeutic candidates for neurodegenerative diseases. Our programs are at different stages of clinical and preclinical development. We discuss our most advanced programs in further detail below.

LRRK2 Inhibitor Program

DNL201 and DNL151 are the two most advanced LRRK2 product candidates in our portfolio, and are potent, selective and brain-penetrant small molecule inhibitors of LRRK2 under investigation for treatment of Parkinson's disease. We recently completed a Phase 1b clinical trial for DNL201 in Parkinson's disease patients both with and without a genetic LRRK2 mutation. DNL151 is currently in a Phase 1 clinical trial in healthy volunteers and a Phase 1b study in Parkinson's disease patients.

LRRK2 is a protein involved in regulating lysosomal function by modifying Rab proteins, which control intracellular lysosomal trafficking. Mutations in the LRRK2 gene that cause Parkinson's disease increase LRRK2 kinase activity leading to excessive phosphorylation of Rab proteins, thereby disrupting normal lysosomal movement and maturation. Inhibition of LRRK2 kinase activity with a LRRK2 kinase inhibitor reduces Rab phosphorylation and restores normal lysosomal function.

Biomarker-Driven Development

We have developed assays that measure pS935 LRRK2 and pRab10 phosphorylation as markers of LRRK2 kinase activity to demonstrate target engagement in humans. Phosphorylation of LRRK2 at serine 935 ("pS935") is a well-established biomarker of LRRK2 kinase activity that has been demonstrated to respond to pharmacological inhibition. Rab10 is a member of the Rab GTPase family involved in endolysosomal function and is a direct substrate of LRRK2 kinase.

To provide greater insight into the effects of LRRK2 inhibitors on lysosomal biology in humans, in addition to pRab10 phosphorylation, we have measured di-22:6-bis(monoacylglycerol)phosphate ("BMP di22:6") in the urine of subjects treated with LRRK2 inhibitors. BMP di22:6 is a lysosomal lipid biomarker that indicates changes in lysosome function associated with LRRK2 inhibition and is elevated in individuals that carry LRRK2 disease-associated mutations.

Results of DNL201 phase 1 clinical study in healthy volunteers

The DNL201 Phase 1 clinical trial in healthy volunteers was completed in July 2018. This was a randomized, double-blind, placebo-controlled, single-center clinical trial in 105 healthy young and 17 healthy elderly subjects 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. In this trial, DNL201 met all objectives including CSF exposure levels and LRRK2 inhibition, as well as evidence of pathway engagement, at doses that were well tolerated. The data from this clinical trial supported our decision to initiate the Phase 1b clinical study in Parkinson’s disease patients.

Results of DNL201 phase 1b clinical study in Parkinson’s disease patients

The DNL201 Phase 1b clinical trial in Parkinson’s disease patients was completed in December 2019, and safety and biomarker data from this study, including biomarkers of lysosomal function, support advancement to the next stage of clinical development (figure 5A below).

This study (NCT03710707) was a 28-day, randomized, placebo controlled Phase 1b clinical trial in patients with mild to moderate Parkinson’s disease, with and without genetic LRRK2 mutations. Its purpose was to evaluate safety, tolerability, pharmacokinetics, pharmacodynamics, and target and pathway engagement biomarkers in multiple oral doses of DNL201. Exploratory endpoints included certain clinical endpoints. The 28 patients dosed in the study were randomized to receive either a low dose of DNL201, a high dose of DNL201, or placebo.

Safety

DNL201 was generally well tolerated at the low dose and the majority of subjects experienced either no or mild adverse events (“AEs”). There was one serious adverse event considered unrelated to drug. At the high dose, the majority of subjects experienced either mild or moderate AEs and there was one severe AE (headache) leading to dose reduction and one study withdrawal (headache and nausea). All treatment-related AEs were manageable and reversible.

Target and Pathway Engagement

The Phase 1b results with DNL201 in patients with Parkinson’s disease met all biomarker goals by demonstrating greater than 50 percent inhibition of pS935 LRRK2 and pRAB10 in blood for both doses tested and improvement of the lysosomal biomarker BMP (22:6-bis-monoacylglycero-phosphate) by 20 percent and 60 percent in urine at the low and high dose, respectively.

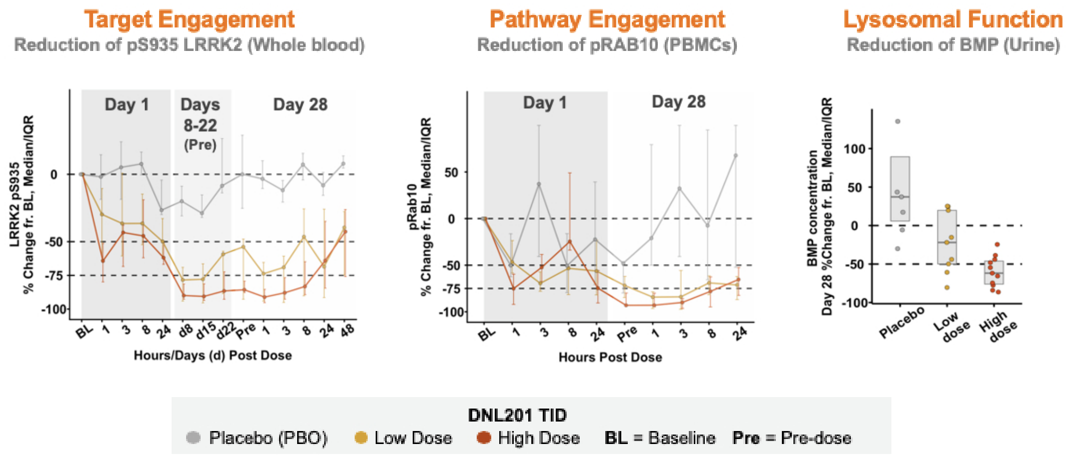

Figure 5A: Left: DNL201 demonstrates: pS935 LRRK2 inhibition, a biomarker of LRRK2 kinase activity and target engagement. M**iddle:** pRab10 inhibition, a biomarker of LRRK2 kinase pathway engagement linked to lysosomal regulation. **Right:** reduction in urinary BMP, an established biomarker of lysosomal dysfunction in biofluids that is elevated in LRRK2 mutation carriers.

Preliminary Results of DNL151 phase 1 clinical study in healthy volunteers

Preliminary results from the ongoing Phase 1 study for DNL151 in healthy volunteers demonstrated an encouraging safety and pharmacokinetic/pharmacodynamic profile (Figure 5B). DNL151 was generally well tolerated at all doses tested, and the majority of subjects experienced either no or mild AEs. Target and pathway engagement of greater than 50 percent and a dose-dependent reduction of BMP in urine of up to 50 percent were observed at clinically relevant doses. Given these positive data, both of the ongoing DNL151 Phase 1 and Phase 1b clinical trials have been expanded to study higher doses.

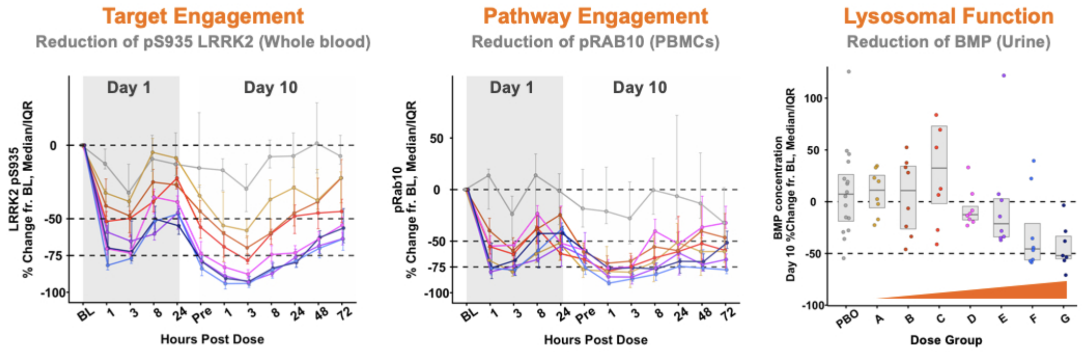

Figure 5B: Left: DNL151 demonstrates: Left-pS935 LRRK2 inhibition, a biomarker of LRRK2 kinase activity and target engagement. **Middle:** pRab10 inhibition, a biomarker of LRRK2 kinase pathway engagement linked to lysosomal regulation. **Right:** reduction in urinary BMP.

Status of DNL151 phase 1b clinical study in Parkinson's disease patients

This study is a 28-day, multicenter, randomized, placebo controlled, double-blind Phase 1b clinical trial in patients with mild-to-moderate Parkinson's disease. Its purpose is to evaluate safety, tolerability, pharmacokinetics, pharmacodynamics, including target and pathway engagement biomarkers as well as certain exploratory clinical endpoints, after multiple oral doses of DNL151. To date, 25 patients have been enrolled in the study, and the protocol has been amended to expand the study with up to 10 additional patients. Final data readout from this trial is expected to be presented in mid-2020.

Future Development Plan

DNL151 is currently in a Phase 1 clinical trial in healthy volunteers and a Phase 1b biomarker study in Parkinson's disease patients. After completion of the ongoing Phase 1 and Phase 1b studies for DNL151 in mid-2020, we will have dosed more than 300 subjects with one of our LRRK2 inhibitors. Upon completion of the ongoing clinical studies, as well as ongoing chronic toxicology studies, we plan to select either DNL201 or DNL151 for advancement into a Phase 2/3 clinical trial.

Other LRRK2 Compounds

Genetic and functional studies have linked LRRK2 and other proteins that modulate lysosomal function to Crohn's disease. Excessive LRRK2 activity leads to a reduction in lysosomal function, which contributes to the inflammation and intestinal dyshomeostasis that are characteristic of this disorder. We have discovered potent and selective small molecule inhibitors of LRRK2 and have selected a lead clinical candidate for treatment of Crohn's disease.

RIPK1 Inhibitor Program

DNL747 is the most advanced product candidate in our receptor interacting serine/threonine protein kinase 1, or RIPK1, inhibitor program, and is a potent, selective and brain-penetrant small molecule RIPK1 inhibitor. As described in more detail in "Business - Licenses and Collaborations" below, we are collaborating with Sanofi on the RIPK1 inhibitor program in neurological diseases, including Alzheimer's disease, ALS and multiple sclerosis ("MS").

RIPK1 is a critical signaling protein in the tumor necrosis factor receptor pathway and is a regulator of inflammation and cell death. Increased RIPK1 activity in the brain drives neuroinflammation and cell necroptosis and contributes to neurodegeneration. RIPK1 inhibition has been shown to have beneficial effects in preclinical models of Alzheimer's disease, ALS and other diseases.

Biomarker-Driven Development

Target engagement has been characterized using a marker of RIPK1 activity, autophosphorylation of RIPK1 at Serine166 (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.

Results of phase 1 clinical study in healthy volunteers

The Phase 1 clinical trial of DNL747 in healthy volunteers was completed in November 2018. This was a randomized, double-blind, placebo-controlled, single-center clinical trial in 56 healthy 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. In this trial, DNL747 met all endpoints, including CSF exposure levels, RIPK1 inhibition, and pathway engagement, at doses that were well tolerated. The data from this clinical trial supported our decision to initiate the Phase 1b clinical studies in patients with ALS and Alzheimer's disease.

Future Development Plan

Together with our partner Sanofi, we have completed enrollment in two Phase 1b patient biomarker studies in ALS and Alzheimer's disease and have initiated an open-label extension, or OLE, study for patients with ALS. Based on final safety and biomarker data for the Phase 1b patient biomarker studies and ongoing chronic toxicology studies, we plan to determine the next steps in the clinical development plan for DNL747 in collaboration with Sanofi.

Other RIPK1 Compounds

As part of our parallel development strategy, we have also developed a number of other structurally diverse CNS-penetrant and peripherally-restricted RIPK1 inhibitor molecules, which are included as part of the collaboration agreement with Sanofi. After DNL747, the most advanced RIPK1 inhibitor molecule is DNL758, a Peripheral Product (as defined below) candidate which is in a Phase 1 clinical trial in healthy volunteers. Sanofi leads all clinical development activities with DNL758 for systemic inflammatory diseases.

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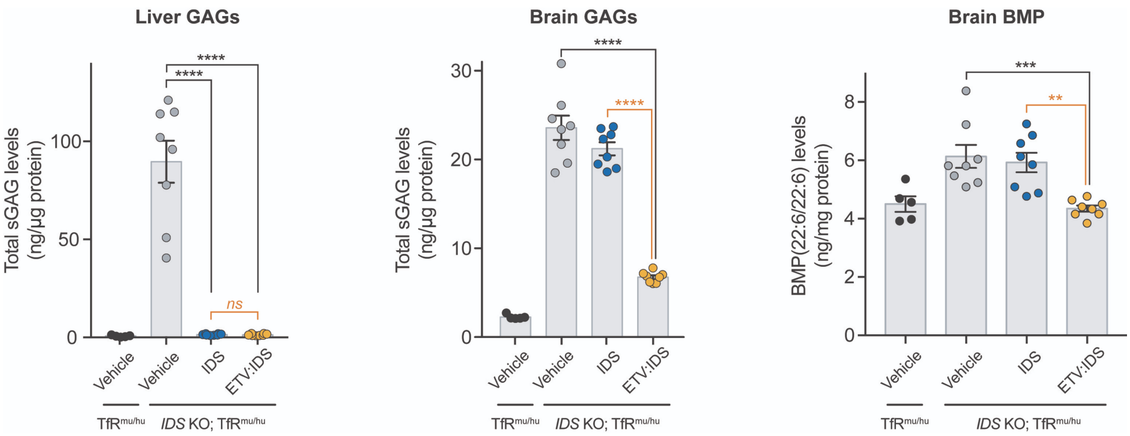
ETV:IDS Enzyme Replacement Therapy Program

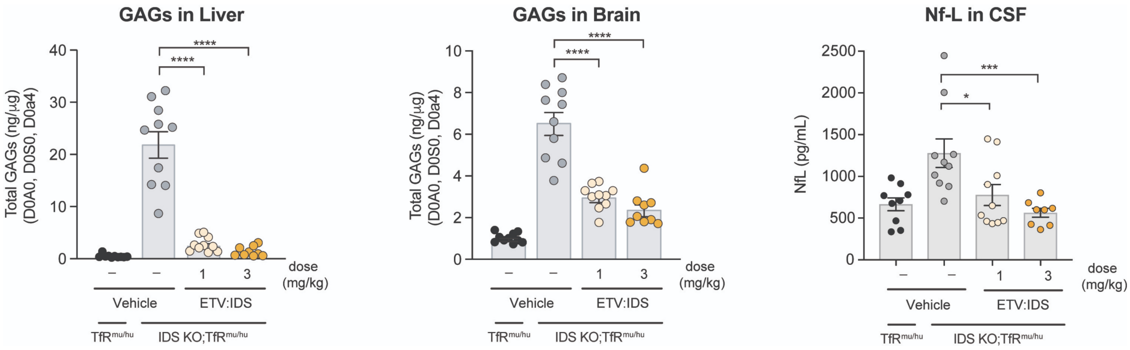
The IDS enzyme is responsible for breaking down the glycosaminoglycans ("GAGs") in the lysosome thereby maintaining lysosomal homeostasis. Genetic defects in IDS lead to a deficiency in IDS enzymatic activity in the lysosome and cause Hunter syndrome, which is characterized by abnormalities in the skeleton, heart, respiratory system, and the brain. Approximately two-thirds of Hunter syndrome patients suffer from central manifestations of the disease, which is characterized by intellectual disability and a progressive cognitive decline that emerges between three and five years of age. Hunter syndrome is currently treated with IV infusions of recombinant IDS protein. These treatments do not efficiently distribute to the brain and, therefore, cannot address the neurological symptoms of the disease. There is a demonstrated need for enzyme replacement therapies ("ERTs") that effectively cross the BBB so as to treat both central and peripheral manifestations of Hunter syndrome and other LSDs.

DNL310 ("ETV:IDS") is an intravenously, centrally administered ERT biotherapeutic enabled by our enzyme transport vehicle ("ETV"), designed to address both central and peripheral manifestations of the disease by restoring IDS and reducing GAGs, both peripherally and in the brain, in patients with Hunter syndrome. We have completed proof of concept short-term dosing studies with administration of comparable activity matched high doses of Elaprase and ETV-IDS (Figure 6A). In addition, we have completed studies with longer term dosing at lower dose levels to evaluate the lowest potential efficacious dose that demonstrates GAG reduction and reduction in NfL, a marker of neuroaxonal injury prevention (Figure 6B)



n=8 per IDS KO; TfR$^{mu/hu}$ group or 5 per TfR$^{mu/hu}$ group, data shown as mean +/- s.e.m.; *** p < 0.001, **** p < 0.0001, ns = not significant

Figure 6A: Left and middle: ETV:IDS reduces GAG levels in the liver in a mouse model of Hunter syndrome, comparable to the reduction seen with IDS, while ETV:IDS significantly reduces GAG levels in the brain as compared to IDS. **Right:** ETV:IDS significantly reverses BMP accumulation, a lipid biomarker, as compared to IDS.



n=10 per TfR$^{mu/hu}$ group, n= 9-10 per IDS KO; TfR$^{mu/hu}$ group; data shown as mean +/- s.e.m.; * p < 0.05, *** p < 0.001, **** p < 0.0001; 13 week dose range study

Figure 6B: 13 weeks IV administration dose range study of therapeutically-relevant doses in a mouse model of Hunter syndrome. **Left and middle:** ETV:IDS reduces levels of GAGs, substrates of the IDS enzyme, in the liver and brain; **Right:** ETV:IDS reduces levels of neurofilament light ("NfL"), a marker of neuronal injury.

Biomarker-Driven Development

We have developed and validated assays to quantify GAGs in CSF and urine of patients receiving DNL310. These assays are designed to measure changes in primary substrate accumulation that is a result of enzyme deficiency in these patients. In addition, we have identified pathway and disease biomarkers that are dysregulated in animal models of Hunter syndrome.

Future Development Plan

The investigational new drug application ("IND") for DNL310 was accepted in January 2020. We plan to initiate a Phase 1/2 study for DNL310 in Hunter syndrome patients in the first half of 2020. DNL310 will be our first therapeutic enabled by our TV BBB platform technology to enter the clinic and we intend to demonstrate proof of concept patient biomarker data for DNL310 by the end of 2020.

EIF2B Program

Mutations in several ALS / FTD degenogenes alter RNA homeostasis and drive chronic cellular stress in these diseases. Activators of EIF2B have demonstrated benefits in resolving cellular integrated stress response ("ISR") and restoring protein translation and RNA metabolism in numerous *in vitro* and *in vivo* models of neurodegenerative disease.

DNL343 is the most advanced product candidate in our EIF2B program, and is a brain penetrant small molecule designed to activate EIF2B function in ALS / FTD.

Biomarker-Driven Development

We have developed assays to measure ATF4 protein and ISR gene expression as proximal pathway markers of EIF2B activity in humans. ATF4 is a transcription factor that modulates ISR gene expression and is upregulated when cellular stress modifies EIF2B activity. These biomarkers have been characterized in *in vitro* assays and in human PBMCs.

Development Plan

We initiated a Phase 1 clinical trial of DNL343 in healthy volunteers in February 2020. The Phase 1 study is a randomized, double-blind, placebo-controlled, single-center clinical trial in 88 healthy subjects to investigate the safety and tolerability of single and multiple ascending oral doses of DNL343 and characterize the PK and PD of DNL343 in plasma and CSF. Initial safety and biomarker results from this study are expected by late 2020.

PTV:PGRN Program

PGRN is a soluble lysosomal protein that has critical functions in lysosomes and an innate immunity in the brain. Loss of function genetic mutations in the gene coding for PRGN, *GRN*, cause FTD by decreasing PGRN levels in the brain. PGRN is a soluble lysosomal protein required to maintain normal lysosomal function.

DNL593 is an intravenously, centrally administered recombinant PGRN biotherapeutic enabled by our protein transport vehicle ("PTV") designed to restore normal levels of PGRN in multiple cell types in the brain without interfering with normal PGRN processing. DNL593 has demonstrated the ability to improve lysosomal function both peripherally and in the brain. DNL593 is currently in IND-enabling studies, and we plan to file an IND or a clinical trial application ("CTA") in 2021. As described in more detail in “Business - Licenses and Collaborations” below, Takeda has the right to opt in to our PTV:PGRN program.

ATV:TREM2 Program

ATV:TREM2 is a therapeutic candidate designed to rescue microglial function in Alzheimer’s disease through modulating the activity of TREM2. Genetic studies suggest that immune dysregulation strongly contributes to the development and progression of Alzheimer’s disease. Microglia, the resident immune cells of the brain, show signs of activation and release of toxic cytokines in patients with Alzheimer’s disease. We have developed TV-enabled anti-TREM2 antibodies that have demonstrated significantly higher brain uptake compared to standard TREM2 antibodies as well as modulation of microglial gene expression in mouse models.

We have developed high affinity antibodies for TREM2 and are currently characterizing lead ATV:TREM2 therapeutic candidates. We plan to file an IND or CTA for this program in 2022. As described in more detail in “Business - Licenses and Collaborations” below, Takeda has the right to opt in to our ATV:TREM2 program.

Our portfolio includes additional preclinical programs, including programs targeting alpha-Synuclein ("ATV:aSyn"), Tau ("ATV:Tau") and SGSH ("ETV:SGSH"), which are enabled by our TV BBB platform technology. In addition to ATV:TREM2 and PTV:PGRN, our ATV:Tau program is partnered with Takeda as described in more detail in “Business - Licenses and Collaborations” below.

Licenses and Collaborations

Takeda Option and Collaboration Agreement

Overview

In January 2018, we entered into the Collaboration Agreement with Takeda ("Takeda Collaboration Agreement"), pursuant to which we granted Takeda an option with respect to our ATV:BACE1/Tau, ATV:TREM2 and PTV:PGRN programs. The Takeda Collaboration Agreement provided that Takeda pay a $40.0 million upfront payment, which was received in February 2018. The Takeda Collaboration Agreement became effective in February 2018 when the requirements of the Hart-Scott-Rodino Antitrust Improvements Act of 1976 were satisfied. In February 2019, we amended the agreement to replace the ATV:BACE1/Tau program with the ATV:Tau program.

Research Phase and Takeda's Option

Under the Takeda Collaboration Agreement and unless we otherwise agree jointly with Takeda, we will be responsible, at our cost, for conducting activities relating to pre-IND development of biologic products directed to the three identified targets and enabled by our BBB delivery technology targeting transferrin receptor during the applicable option period. The option period continues for each target until the first biologic product candidate directed to the relevant target is IND-ready or about five years after selection of the target, whichever is earlier.

Takeda is obligated to pay us up to an aggregate of $25.0 million with respect to each of the three programs under the Takeda Collaboration Agreement directed to a target and based upon the achievement of certain preclinical milestone events, up to $75.0 million in total, of which $5.0 million was received when the Takeda Collaboration Agreement became effective. Additional payments totaling $10.0 million became due based on the achievement of certain preclinical milestone events in 2018, of which $5.0 million was received in November 2018 and $5.0 million was received in February 2019.

Collaboration Activities Following Takeda's Option Exercise

If Takeda exercises its option with respect to a particular target and collaboration program (i.e., the biologic products directed to the target for which Takeda has exercised its option), then Takeda will have the right to develop and commercialize, jointly with us, a specified number of biologic products enabled by our blood-brain barrier delivery technology that were developed during the option period and which are directed to the relevant target, and we will grant to Takeda a co-exclusive license under the intellectual property we control related to those biologic products.

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

In addition, if Takeda exercises its option for all three collaboration programs, Takeda may be obligated to pay us up to an aggregate of $407.5 million upon achievement of certain clinical milestone events and up to an aggregate of $300.0 million in regulatory milestone events relating to receipt of regulatory approval in the United States, certain European countries and Japan. Further, Takeda may also be obligated to pay us up to $75.0 million per biologic product upon achievement of a certain sales-based milestone, or an aggregate of $225.0 million if one biologic product from each program achieves the milestone.

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

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

We have the right to lead all manufacturing activities for all collaboration programs for which the parties are sharing costs and profits.

Exclusivity

During the option period for a particular target and, if the applicable option is exercised by Takeda (unless the Takeda Collaboration Agreement is terminated earlier), until expiration of an agreed period of time after the first regulatory approval in the United States or Europe of a biologic product within the applicable collaboration program, neither party may conduct clinical or commercial activities involving antibodies or protein-based therapeutic products directed to the same target (or in the case of a bi-specific program, the same combination of targets) that have an intended therapeutic effect in diseases and conditions of the CNS (including lysosomal storage diseases), except to the extent permitted under the Takeda Collaboration Agreement.

Termination

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

Following any termination of the Takeda Collaboration Agreement with respect to a particular collaboration program or the Takeda Collaboration Agreement in its entirety, our rights to each terminated collaboration program will revert to us, Takeda will grant us a license to intellectual property owned by Takeda with respect to such collaboration program (which could be subject to certain royalty payments that would be negotiated at the time of such a termination) and, unless the termination was by Takeda on the basis of a material safety event, Takeda will conduct certain development, manufacturing and commercialization wind-down activities.

Common Stock Purchase Agreement

Pursuant to the terms of the Takeda Collaboration Agreement, we entered into a common stock purchase agreement (the “Purchase Agreement”) with Takeda in January 2018, pursuant to which we agreed to issue and sell, and Takeda agreed to purchase, 4,214,559 shares of our common stock (the “Shares”) for an aggregate purchase price of $110.0 million pursuant to the terms and conditions thereof. We closed the sale of the Shares to Takeda in February 2018.

We and Takeda also entered into a standstill and stock restriction agreement (the “Standstill Agreement”). Pursuant to the terms of the Standstill Agreement, Takeda agreed to certain transfer and standstill restrictions, including a restriction on acquiring more than 10% of our capital stock, for a specified period of time following the closing of the sale of the Shares to Takeda, or earlier upon our change of control or, with respect to the transfer restrictions, termination of the Takeda Collaboration Agreement. In addition, Takeda is entitled to certain registration rights with respect to the Shares following termination of the transfer restrictions if the Shares cannot be resold without restriction pursuant to Rule 144 promulgated under the Securities Act of 1933, as amended.

Sanofi Collaboration and License Agreement

Overview

In October 2018, we entered into the Collaboration Agreement with Genzyme Corporation, a wholly owned subsidiary of Sanofi S.A. ("Sanofi") pursuant to which certain small molecule compounds that bind to and inhibit RIPK1 (“RIPK1 Inhibitors”) contributed by Sanofi and by Denali will be developed and commercialized. The Sanofi Collaboration Agreement became effective in November 2018 when the requirements of the Hart-Scott-Rodino Antitrust Improvements Act of 1976 were satisfied.

Denali and Sanofi plan to jointly develop products containing RIPK1 Inhibitors for neurological indications, such as Alzheimer’s disease, ALS and MS, and Sanofi plans to develop and commercialize products containing RIPK1 Inhibitors for systemic inflammatory indications, such as rheumatoid arthritis and psoriasis.

The Sanofi Collaboration Agreement includes Denali’s and Sanofi’s RIPK1 Inhibitors that measurably penetrate the blood-brain barrier ("CNS Products"), and Denali’s and Sanofi’s RIPK1 Inhibitors that do not measurably penetrate the blood-brain barrier ("Peripheral Products"). The two most advanced RIPK1 Inhibitors in the collaboration are DNL747, a CNS Product that was discovered by Denali and is currently in two Phase 1b studies in patients with ALS and Alzheimer’s disease, and DNL758, a Peripheral Product discovered by Denali which is currently in a Phase 1 clinical trial in healthy volunteers.

License Grant

Under the Sanofi Collaboration Agreement, we granted Sanofi an exclusive, worldwide license under intellectual property that we control related to Denali’s RIPK1 Inhibitors, including certain intellectual property licensed to us by an academic institution.

Payments

When the Sanofi Collaboration Agreement became effective in November 2018, Sanofi paid us $125.0 million upfront, and in August 2019, Sanofi paid us $10.0 million for the milestone triggered by the commencement of a DNL758 Phase 1 clinical trial in healthy volunteers. Under the Sanofi Collaboration Agreement, Sanofi is required to make milestone payments up to approximately $1.1 billion upon achievement of certain clinical, regulatory and sales milestone events. Such milestone payments include $215.0 million in clinical milestone payments and $385.0 million in regulatory milestone payments for CNS Products, as defined, that are developed and approved in the United States, by the European Medicines Agency ("EMA") and in Japan for three indications, including Alzheimer's disease. These milestones also include $120.0 million in clinical milestone payments, $175.0 million in regulatory milestone payments and $200.0 million in commercial milestone payments for Peripheral Products, as defined, that are developed and approved in the United States, by the EMA and in Japan for three indications.

Denali will share profits and losses equally with Sanofi for CNS Products sold in the United States and China, and receive royalties on net sales for CNS Products sold outside of the United States and China and for Peripheral Products sold worldwide, each as further described below.

RIPK1 Inhibitors contributed by Sanofi and developed and commercialized under the Sanofi Collaboration Agreement will be subject to lower milestone and royalty payments to us compared to RIPK1 Inhibitors contributed by us. We will also retain responsibility for certain payment obligations under our agreement with an academic institution which licensed certain intellectual property to us that we are sublicensing to Sanofi under the Sanofi Collaboration Agreement.

Program for Development and Commercialization of CNS Products

Denali and Sanofi will jointly develop CNS Products pursuant to a global development plan ("CNS Development Plan"). We will be responsible, at our cost, for conducting Phase 1 and Phase 2 trials for CNS Products for Alzheimer's disease and any activities required to support such clinical trials and specific for Alzheimer's disease. We are conducting and will complete, at Sanofi's cost, a Phase 1b trial of DNL747 for ALS. Sanofi will be responsible, at its cost, for all other Phase 1 and Phase 2 trials for CNS Products, including for multiple sclerosis. Sanofi will lead the conduct of all Phase 3 and later stage development trials for CNS Products, with Sanofi and Denali funding 70% and 30% of such costs, respectively. The Sanofi Collaboration Agreement contains certain protections for us with respect to Phase 3 development costs not included in the initial budget for the CNS Development Plan agreed by the parties, including a deferral mechanism for costs incurred above the budgeted amounts for such trials and for costs incurred in respect of Phase 3 and other clinical trials not contemplated in the initial CNS Development Plan. In addition, we have the ability to opt out of the cost-profit sharing provisions of the Sanofi Collaboration Agreement, as further described below.

Sanofi will lead commercialization activities globally for CNS Products. We may elect to conduct certain co-commercialization activities outside of MS with respect to each CNS Product in the United States and/or China, provided that the cost-profit sharing provisions of the Sanofi Collaboration Agreement for the relevant CNS Product are still in effect, as further described below.

We may opt out of the cost-profit sharing provisions of the Sanofi Collaboration Agreement for CNS Products in the United States and China on a CNS product-by-CNS Product and country-by-country basis. Sanofi may also terminate our cost-profit sharing provisions of the Sanofi Collaboration Agreement in its entirety if, following notice from Sanofi and a cure period, we fail to satisfy our cost-sharing obligations. After such an opt out by us or termination by Sanofi, we will no longer be obligated to share in the development and commercialization costs for the applicable CNS Products and we will not share in the applicable profits from such CNS Products. Instead, we will be entitled to receive tiered royalties on net sales of the applicable CNS Products in the relevant country (or countries). The royalty rates will be a percentage in the low double digits to mid-teens, but may increase to the mid-teens to low-twenties percentages for all countries in which Sanofi is paying royalties on the applicable CNS Products, if we have met certain co-funding thresholds at the time of our election or Sanofi's termination of our cost-profit sharing rights and obligations.

Program for Development and Commercialization of Peripheral Products

Sanofi will be responsible, at its cost, for conducting activities relating to the development and commercialization of all Peripheral Products.

Sanofi will lead commercialization activities globally for Peripheral Products. We will be entitled to receive tiered royalties in the low- to mid- teen percentages on net sales of Peripheral Products.

Manufacturing

Sanofi will be responsible for delivering all supplies for clinical trials and commercial production for CNS Products and Peripheral Products, except that we will deliver such supplies for the currently in-progress Phase 1b trials for DNL747 and the Phase 1 trial for DNL758.

Royalty Term

For any CNS Product with respect to any country for which Sanofi is required to pay royalties on net sales and for each Peripheral Product, Sanofi will pay royalties to us on a country-by-country basis until the latest of (i) the expiration of certain patents covering the relevant product, (ii) the expiration of all regulatory exclusivity for that product in the applicable country, and (iii) an agreed period of time after the first commercial sale of that product in the applicable country. If, in a particular country, a CNS Product for which Sanofi is required to pay royalties or a Peripheral Product is not covered by specified patent rights in that country or net sales in that country decrease below specified thresholds as a result of generic competition, Sanofi's royalty obligations in the applicable country would be reduced or would terminate as specified in the Sanofi Collaboration Agreement.

Exclusivity

During the term of the Sanofi Collaboration Agreement, neither Denali nor Sanofi may conduct IND-enabling, clinical or commercial activities involving any RIPK1 Inhibitor, anywhere in the world, unless the RIPK1 Inhibitor is included by Denali or Sanofi, as the case may be, under the collaboration and only to the extent such activity is permitted under the Sanofi Collaboration Agreement.

Termination

Each party may terminate the Sanofi Collaboration Agreement in its entirety, or with respect to a particular program (i.e., the CNS Products program or Peripheral Products program), as applicable, if the other party remains in material breach of the Sanofi Collaboration Agreement following a cure period to remedy the material breach. After giving a specified amount of prior notice to us, Sanofi may terminate the Sanofi Collaboration Agreement for convenience in its entirety, with respect to any particular program, or with respect to one or more specified regions of the world. Sanofi may also terminate the Sanofi Collaboration Agreement with respect to any program or a particular RIPK1 Inhibitor if a material safety event has occurred and cessation of all development and commercialization of all RIPK1 Inhibitors in the affected program or the affected RIPK1 Inhibitor is recommended. Denali and Sanofi may each terminate the Sanofi Collaboration Agreement in its entirety if the other party is declared insolvent or in similar financial distress or if, subject to a specified cure period, the other party challenges any patents licensed to it under the Sanofi Collaboration Agreement.

Following any termination of the Sanofi Collaboration Agreement with respect to a particular program or a particular region (or regions) of the world or termination of the Sanofi Collaboration Agreement in its entirety, our rights to each of our RIPK1 Inhibitors that were licensed to Sanofi will revert to us. Sanofi will conduct certain development, manufacturing and commercialization activities on a transitional basis following termination of the Sanofi Collaboration Agreement, as outlined in the Sanofi Collaboration Agreement or agreed by Sanofi, depending upon the basis for the applicable termination.

If the Sanofi Collaboration Agreement is terminated for any reason other than by Sanofi for our material uncured breach, our insolvency or our challenge to any of the patents licensed to us by Sanofi, Sanofi will grant us an exclusive license to certain intellectual property controlled by Sanofi with respect to such RIPK1 Inhibitors (which could be subject to low single digit royalties payable to Sanofi).

F-star License and Collaboration Agreement

Overview

In August 2016, we entered into a license and collaboration agreement (“F-star Collaboration Agreement”) with F-star Gamma Limited (“F-star Gamma”), F-star Biotechnologische Forschungs-Und Entwicklungsges m.b.H ("F-star GmbH") and F-star Biotechnology Limited ("F-star Ltd") (collectively "F-star"). The goal of the collaboration was 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 was designed to leverage F-star’s modular antibody technology and our expertise in the development of therapies for neurodegenerative diseases. 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 (the “Option Agreement”).

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

As a result of the Acquisition, F-star Gamma became a wholly-owned subsidiary of the Company and we changed the entity’s name to Denali BBB Holding Limited. In addition, we became a direct licensee of certain intellectual property of F-star Ltd (by way of the Company’s assumption of F-star Gamma’s license agreement with F-star Ltd, dated August 24, 2016, (the “F-star Gamma License”)). We made initial exercise payments under the Purchase Agreement and the F-star Gamma License of $18.0 million in the aggregate, less the net liabilities of F-star Gamma, which were approximately $0.2 million. In addition, we are required to make future contingent payments, to F-star Ltd and the former shareholders of F-star Gamma, up to a maximum amount of $447.0 million in the aggregate upon the achievement of certain defined preclinical, clinical, regulatory and commercial milestones. These include up to $27.0 million in preclinical contingent payments, $50.0 million in clinical contingent payments, $120.0 million in regulatory contingent payments and $250.0 million in commercial contingent payments. The amount of the contingent payments will vary based on whether F-star delivers an Fcab (constant Fc-domains with antigen-binding activity) that meets pre-defined criteria and whether the Fcab has been identified solely by us or solely by F-star or jointly by us and F-star. In June 2019, we made a payment of $1.5 million to F-star Ltd upon the achievement of a specified preclinical milestone in the Company's ETV:IDS program.

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

We are also responsible for certain research costs incurred by F-star Ltd in conducting activities under an agreed development plan for each Fcab, for up to 24 months after the target Fcab is accepted.

Genentech Exclusive License Agreement

In June 2016, we entered into an exclusive license agreement with Genentech, Inc. (“Genentech”). The agreement gives us access to Genentech’s LRRK2 inhibitor small molecule program for Parkinson’s disease. Under the agreement, Genentech granted us (i) an exclusive, worldwide, sublicensable 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, sublicensable 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. These milestones include up to $37.5 million in clinical milestone payments, $102.5 million in regulatory milestone payments and $175.0 million in commercial milestone payments. 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.

Manufacturing

We believe it is important to our business success to have a reliable, high-quality preclinical and clinical drug supply chain. 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 development and manufacturing organizations ("CDMOs"), to manufacture and supply our preclinical and clinical materials used during the development of our product candidates. We have established relationships with several CDMOs, including Lonza Sales AG ("Lonza"), WuXi Biologics Limited and Thermo Fisher Scientific. Effective September 2017, we entered into a development and manufacturing services agreement with Lonza, which we have subsequently amended to add scope of work. 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.

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.

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, including China. For commercial activities in the rest of the world, we expect to rely on partnerships, including those with Takeda and Sanofi, 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, Roche (including Genentech, its wholly owned subsidiary), Alector and AbbVie 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, Voyager Therapeutics, Sage Therapeutics, Sanofi, Biogen, AstraZeneca, Lundbeck, Takeda and AbbVie 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 Biogen, Genentech, AL-S Pharma and Novartis 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, RegenxBio, Sangamo, Sanofi, Takeda and Ultragenyx 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.

As of December 31, 2019, our owned and licensed patent portfolio includes over 900 patents and patent applications, including over 30 licensed U.S. issued patents and 9 owned U.S. issued patents, covering certain aspects of our proprietary technology, our product candidates, and related inventions and improvements. The patent portfolio also includes over 500 licensed patents issued in jurisdictions outside of the United States, and over 200 owned patent applications pending in jurisdictions outside of the United States that, in many cases, are counterparts to the foregoing U.S. patents and patent applications. For our product candidates and our BBB platform technology, we generally pursue or in-license patent protection covering compositions of matter, methods of use, and manufacture. For example, we own patent applications in the United States and internationally that are directed to the composition of matter of certain antibodies and small molecule product candidates that we intend to develop or are developing, as well as the Fc domain portion of our BBB platform technology.

For our BBB platform technology we own pending patent applications directed to the composition and sequences of our TfR-binding TVs and two issued U.S. patents, as well as pending patent applications, to other BBB platform technology. Furthermore, we own patent applications directed to our ETV:IDS, ATV:TREM2, and PTV:PGRN programs. In addition, we license multiple patent families from F-star, the earliest issued patents of which are expected to expire in 2026, not including any patent term adjustments and any patent term extensions.

For our LRRK2 program, we license multiple patent families from Genentech directed to, among other things, DNL201, DNL151 and other related compounds, which are expected to expire in 2031, not including any patent term adjustments and any patent term extensions. Furthermore, we own patent families that have projected expiration dates in 2038 or later, not accounting for any patent term adjustments and any patent term extensions. We also own an issued U.S. patent, which is expected to expire in 2037, not including any patent term adjustments and any patent term extensions, and pending patent applications in jurisdictions outside the U.S. directed to the composition of matter of DNL151.

For our RIPK1 program, we own three issued U.S. patents, which are expected to expire in 2037, not including any patent term adjustments and any patent term extensions and pending patent applications, which are directed to the composition of matter of DNL747 as well as other RIPK1 inhibitor compounds.

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 United States Patent and Trademark Office (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 ("FDCA"), and its implementing regulations, and biologics under the FDCA, the Public Health Service Act ("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 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 ("NDA"), or a biologics license application ("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 ("GLP"), requirements;
- Submission of an IND to the FDA, or a CTA to the EMA, one of which must become effective before human clinical trials may begin;
- Approval by an independent institutional review board ("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 or CTA regulations, good clinical practice ("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 ("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 ("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. 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 or severity 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 and/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 ("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, 2019, the user fee for an application requiring clinical data, such as an NDA or BLA, is $2,588,478. PDUFA also imposes an annual program fee for each marketed human drug or biologic of $309,915. 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 for an orphan indication submission.

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 may be 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 the combination of 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.

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 facilitate an efficient drug development program.

Any product submitted to the FDA for marketing, including under a fast track or breakthrough therapy designation 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 be eligible for accelerated approval, if it treats a serious or life-threatening condition and generally provides a meaningful advantage over available therapies based on 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 ("IMM"), that is reasonably likely to predict an effect on IMM or other clinical benefit. As a condition of accelerated approval, the FDA requires that a sponsor of a drug or biologic receiving accelerated approval subsequently provide additional data confirming the anticipated clinical benefit, for example by performing adequate and well-controlled post-marketing clinical trials. If clinical benefit is not confirmed, accelerated approval may be revoked. 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.

Fast track designation, breakthrough therapy designation, priority review, and 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 ("PPACA"), Affordable Care Act ("ACA"), signed into law in 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009 ("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 ("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 ("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 ("NCA"), and one or more Ethics Committees ("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. Clinical Trials Regulation EU No 536/2014, which is expected to be enacted, will ensure 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 ("EEA"), which is comprised of the 27 Member States of the European Union, plus Norway, Iceland and Liechtenstein, medicinal products can only be commercialized after obtaining a Marketing Authorization ("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 ("CHMP"), of the 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 may also apply 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 ("RMS"). The competent authority of the RMS prepares a draft assessment report, a draft summary of the product characteristics ("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 assess 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 ("AMP"), to 23.1% of AMP and adding a new rebate calculation for "line extensions" (e.g., 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 ("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 ("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 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.

Financial Information about Segments

We manage our operations as a single reportable segment for the purposes of assessing performance and making operating decisions. See "Note 1 - Significant Accounting Policies" in the notes to the consolidated financial statements included elsewhere in this Annual Report on Form 10-K.

Employees

As of December 31, 2019, we had 261 employees, all of whom were full-time, and approximately two-thirds of which hold Ph.D. or M.D. degrees. Of these full-time employees, 210 were engaged in research and development activities and 51 were engaged in finance, legal, business development, human resources, information technology, facilities and other general administrative functions. Substantially all of our employees are located in South San Francisco, California. None of our employees is represented by a labor union or covered by a collective bargaining agreement. We consider our relations with our employees to be good.

Corporate Information

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

We file electronically with the SEC our annual reports on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act. We make available on our website at www.denalitherapeutics.com, free of charge, copies of these reports, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. The public may read or copy any materials we file with the SEC at the SEC's Public Reference Room at 100 F Street NE, Washington, D.C. 20549. The public may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC maintains a website that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC. The address of that website is www.sec.gov. The information in or accessible through the SEC and our website or social media sites does not constitute part of this Annual Report on Form 10-K or any other report or document we file with the SEC, and any references to our website and social media sites are intended to be inactive textual references only.

We use Denali Therapeutics®, the Denali Therapeutics logo, and other marks as trademarks in the United States and other countries. This Annual Report on Form 10-K 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 Annual Report on Form 10-K, 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.

ITEM 1A. RISK FACTORS

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

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 very limited operating history, focused on developing therapeutics for neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis ("ALS"). We commenced operations in May 2015, have no products approved for commercial sale and have not generated any revenue from product sales. Drug development is a highly uncertain undertaking and involves a substantial degree of risk. We are in Phase 1 or 1b clinical trials for our LRRK2, RIPK1 and EIF2B programs and have not initiated clinical trials for any of our other current product candidates. To date, we have not initiated or completed a pivotal clinical trial, obtained marketing approval for any product candidates, manufactured a commercial scale product, or arranged for a third party to do so on our behalf, or conducted sales and marketing activities necessary for successful product commercialization. Our short operating history as a company makes any assessment of our future success and viability subject to significant uncertainty. We will encounter risks and difficulties frequently experienced by early-stage biopharmaceutical companies in rapidly evolving fields, and we have not yet demonstrated an ability to successfully overcome such risks and difficulties. If we do not address these risks and difficulties successfully, our business will suffer.

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

We have incurred significant net losses since our inception, including net losses of $197.6 million, $36.2 million, and $88.2 million for the years ended December 31, 2019, 2018 and 2017, respectively. As of December 31, 2019, we had an accumulated deficit of $425.6 million.

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

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

- continue our research and discovery activities;
- progress our current and any future product candidates through preclinical and clinical development;
- initiate and conduct additional preclinical, clinical or other studies for our product candidates;
- work with our contract manufacturers to scale up the manufacturing processes for our product candidates or, in the future, establish and operate a manufacturing facility;
- change or add additional contract manufacturers or suppliers;
- seek regulatory approvals and marketing authorizations for our product candidates;
- establish sales, marketing and distribution infrastructure to commercialize any products for which we obtain approval;
- acquire or in-license product candidates, intellectual property and technologies;
- make milestone, royalty or other payments due under any license or collaboration agreements;
- obtain, maintain, protect and enforce our intellectual property portfolio, including intellectual property obtained through license agreements;
- attract, hire and retain qualified personnel;
- provide additional internal infrastructure to support our continued research and development operations and any planned commercialization efforts in the future;
- experience any delays or encounter other issues related to our operations;
- meet the requirements and demands of being a public company; and
- defend against any product liability claims or other lawsuits related to our products.

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

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

We have no products approved for commercial sale and have not generated any revenue from product sales. To obtain revenue from the sales of our product candidates that are significant or large enough to achieve profitability, we must succeed, either alone or with third parties, in developing, obtaining regulatory approval for, manufacturing and marketing therapies with significant commercial success.

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 ("FDA"), or foreign regulatory agencies, to perform studies in addition to those that we currently anticipate, or if there are any delays in any of our or our future collaborators' clinical trials or the development of any of our product candidates. Even if one or more of our product candidates is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate and ongoing compliance efforts.

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

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

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

Our operations have required substantial amounts of cash since inception. To date, we have financed our operations primarily through the issuance and sale of convertible preferred stock, the proceeds from our initial public offering ("IPO") and follow on offering completed in January 2020, and cash proceeds under our Takeda Collaboration Agreement and Sanofi Collaboration Agreement. We are currently advancing four product candidates, DNL201, DNL151, DNL747, and DNL343 through clinical development, expect to initiate clinical trials for one additional product candidate, DNL310, 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, and continue to advance our programs through preclinical and clinical development. 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.

As of December 31, 2019, we had $455.2 million in cash, cash equivalents and marketable securities. We believe that our existing cash, cash equivalents and marketable securities will be sufficient to fund our projected operations through at least the next 12 months. Our estimate as to how long we expect our existing cash, cash equivalents and marketable securities to be available to fund our operations is based on assumptions that may be proved inaccurate, and we could use our available capital resources sooner than we currently expect. In addition, changing circumstances may cause us to increase our spending significantly faster than we currently anticipate, and we may need to spend more money than currently expected because of circumstances beyond our control. We may need to raise additional funds sooner than we anticipate if we choose to expand more rapidly than we presently anticipate.

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

We have a diversified portfolio with fifteen programs. These programs require significant capital investment. Our programs are at various stages of research, discovery, preclinical and early clinical development. We seek to maintain a process of prioritization and resource allocation to maintain an optimal balance between aggressively advancing lead programs and ensuring replenishment of our portfolio. We regularly review the programs in our portfolio, and terminate those programs which do not meet our development criteria, which we have done a number of times in the past.

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, results of operations and growth prospects could be materially adversely affected. As a result, we may fail to capitalize on viable commercial products or profitable market opportunities, be required to forego or delay pursuit of opportunities with other product candidates or other diseases and disease pathways that may later prove to have greater commercial potential than those we choose to pursue, or relinquish valuable rights to such product candidates through collaboration, licensing or other royalty arrangements in cases in which it would have been advantageous for us to invest additional resources to retain sole development and commercialization rights.

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

Research and development of biopharmaceutical products is inherently risky. We are heavily dependent on the successful development of our BBB platform technology and the programs currently in our pipeline, 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, 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. We have previously discontinued the development of certain molecules prior to completion of preclinical development because we did not believe they met our criteria for potential clinical success. 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 ("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 time frame 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, business, financial condition, results of operations and growth prospects 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 several programs in the research, discovery and preclinical stages of development. Identifying, developing, obtaining regulatory approval and commercializing additional product candidates for the treatment of neurodegenerative diseases will require substantial additional funding and is prone to the risks of failure inherent in drug development. We cannot provide you any assurance that we will be able to successfully identify or acquire additional product candidates, advance any of these additional product candidates through the development process, successfully commercialize any such additional product candidates, if approved, or assemble sufficient resources to identify, acquire, develop or, if approved, commercialize additional product candidates. If we are unable to successfully identify, acquire, develop and commercialize additional product candidates, our commercial opportunity may be limited.

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

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

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

Clinical testing is expensive, time consuming, and subject to uncertainty. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. We cannot be sure that submission of an IND, or a CTA, will result in the FDA 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 ("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 ("IRB") approval at each clinical trial site;

- imposition of a temporary or permanent clinical hold by regulatory agencies for a number of reasons, including after review of an IND or amendment, CTA or amendment, or equivalent application or amendment; as a result of a new safety finding that presents unreasonable risk to clinical trial participants; a negative finding from an inspection of our clinical trial operations or study sites; developments on trials conducted by competitors for related technology that raises FDA or EMA concerns about risk to patients of the technology broadly; or if the FDA or EMA finds that the investigational protocol or plan is clearly deficient to meet its stated objectives;

- delays in identifying, recruiting and enrolling suitable patients to participate in our clinical trials, and delays caused by patients withdrawing from clinical trials or failing to return for post-treatment follow-up;

- difficulty collaborating with patient groups and investigators;

- failure by our CROs, other third parties, or us to adhere to clinical trial requirements;

- failure to perform in accordance with the FDA's or any other regulatory authority's current good clinical practices ("cGCPs") requirements, or applicable EMA or other regulatory guidelines in other countries;

- occurrence of adverse events associated with the product candidate that are viewed to outweigh its potential benefits;

- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols;

- changes in the standard of care on which a clinical development plan was based, which may require new or additional trials;

- the cost of clinical trials of our product candidates being greater than we anticipate;

- clinical trials of our product candidates producing negative or inconclusive results, which may result in our deciding, or regulators requiring us, to conduct additional clinical trials or abandon product development programs;

- transfer of manufacturing processes from our academic collaborators to larger-scale facilities operated by a CDMO or by us, and delays or failure by our CDMOs 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.

DNL201, one of the most advanced LRRK2 product candidates in our portfolio, recently completed a Phase 1b clinical trial in Parkinson's disease patients with and without the genetic LRRK2 mutation. This program was previously subject to a partial clinical hold due to preclinical toxicity data. The partial clinical hold was removed in December 2017 based on additional clinical and preclinical data provided to the FDA. Our other clinical stage product candidates are DNL747, for ALS and Alzheimer's disease patients, DNL151 for Parkinson's disease patients, DNL343 for ALS and FTD, and DNL310 for Hunter syndrome. In the nonclinical safety studies for these product candidates, toxicities were observed at high doses in rat and/or cynomolgus monkey above doses and exposures that will be tested in the clinic. In our recently completed Phase 1b clinical trial of DNL201 in patients with Parkinson’s disease, there was one SAE considered unrelated to drug, and at the high dose, there was one severe AE (headache) leading to dose reduction and one study withdrawal (headache and nausea). We cannot assure you that DNL201, DNL747, DNL151, DNL343 and DNL310, 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 reveal significant adverse events, toxicities, or other side effects and 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. Open-label extension studies may also extend the timing and increase the cost of clinical development substantially. 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, results of operations and growth prospects.

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.

Interim, topline and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available, and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may publicly disclose preliminary, interim or topline data from our clinical trials. These interim updates are based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the topline results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Topline data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, topline data should be viewed with caution until the final data are available. In addition, we may report interim analyses of only certain endpoints rather than all endpoints. Interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Adverse changes between interim data and final data could significantly harm our business and prospects. Further, additional disclosure of interim data by us or by our competitors in the future could result in volatility in the price of our common stock.

Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate and our company in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is typically selected from a more extensive amount of available information. You or others may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise regarding a particular product candidate or our business. If the preliminary or topline data that we report differ from late, final or actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize our product candidates may be harmed, which could harm our business, financial condition, results of operations and prospects.

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, Alector, AstraZeneca, Biogen, Celgene, Eli Lilly, E-Scape Bio, GlaxoSmithKline, Ionis, JCR Pharmaceuticals, Johnson & Johnson, Novartis, Roche, Sanofi and Takeda. In addition to competition from other companies targeting neurodegenerative indications, any products we may develop may also face competition from other types of therapies, such as gene-editing therapies.

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

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 ("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 CDMOs 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 ("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 (the "Hatch-Waxman Act"), a pharmaceutical manufacturer may file an abbreviated new drug application ("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 ("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 ("BLA"), pathway. The Biologics Price Competition and Innovation Act of 2009 (the "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 in an initial or subsequent indication for many reasons, including but not limited to the following:

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

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

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

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

Our most advanced product candidates, DNL201, DNL747, DNL151, DNL343 and DNL310 are currently our only clinical stage product candidates. In our recently completed Phase 1b clinical trial of DNL201 in patients with Parkinson's disease, there was one SAE considered unrelated to drug, and at the high dose, there was one severe AE (headache) leading to dose reduction and one study withdrawal (headache and nausea). Adverse events and other side effects may result from higher dosing, repeated dosing and/or longer-term exposure to DNL201, DNL747, DNL151, DNL343 and/or DNL310 and could lead to delays and/or termination of the development of these product candidates.

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

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

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

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

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, financial condition, results of operations, and growth 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 ("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; and/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. In February 2019, the FDA granted orphan drug designation for our DNL310 program in Hunter syndrome. We plan to seek orphan drug designations for some other 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 though DNL310 has been granted orphan drug designation and 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 ("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 ("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 ("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.

Our business is subject to complex and evolving U.S. and foreign laws and regulations, information security policies and contractual obligations relating to privacy and data protection, including the use, processing, and cross-border transfer of personal information. These laws and regulations are subject to change and uncertain interpretation, and could result in claims, changes to our business practices, or monetary penalties, and otherwise may harm our business.

We receive, generate and store significant and increasing volumes of sensitive information and business-critical information, including employee and personal data (including protected health information), research and development information, commercial information, and business and financial information. We heavily rely on external security and infrastructure vendors to manage our information technology systems and data centers. We face a number of risks relative to protecting this critical information, including loss of access risk, inappropriate use or disclosure, inappropriate modification, and the risk of our being unable to adequately monitor, audit and modify our controls over our critical information. This risk extends to the third-party vendors and subcontractors we use to manage this sensitive data.

A wide variety of provincial, state, national, and international laws, and regulations apply to the collection, use, retention, protection, disclosure, transfer and other processing of personal data. These data protection and privacy-related laws and regulations are evolving and may result in ever-increasing regulatory and public scrutiny and escalating levels of enforcement and sanctions. For example, the collection and use of personal data in the European Union are governed by the European Union General Data Protection Regulation ("GDPR"), which became fully effective on May 25, 2018. The GDPR imposes stringent data protection requirements, including, for example, more robust disclosures to individuals and a strengthened individual data rights regime, shortened timelines for data breach notifications, limitations on retention of information, increased requirements pertaining to special categories of data, such as health data, and additional obligations when we contract with third-party processors in connection with the processing of the personal data. The GDPR also imposes strict rules on the transfer of personal data out of the European Union to the United States and other third countries and in the context of clinical trials, we currently rely on patient informed consent as the legal basis for such transfers. In addition, the GDPR provides that European Union member states may make their own further laws and regulations limiting the processing of personal data, including genetic, biometric or health data. The GDPR provides for penalties for noncompliance of up to the greater of €20 million or four percent of worldwide annual revenues. The GDPR applies extraterritorially, and we may be subject to the GDPR because of our data processing activities that involve the personal data of individuals located in the European Union, such as in connection with any European Union clinical trials. GDPR regulations may impose additional responsibility and liability in relation to the personal data that we process and we may be required to put in place additional mechanisms to ensure compliance with the new data protection rules. This may be onerous and may interrupt or delay our development activities, and adversely affect our business, financial condition, results of operations and prospects.

Further, various states, such as California and Massachusetts, have implemented similar privacy laws and regulations that impose restrictive requirements regulating the use and disclosure of health information and other personally identifiable information. These laws and regulations are not necessarily preempted by HIPAA, particularly if a state affords greater protection to individuals than HIPAA. Where state laws are more protective, we have to comply with the stricter provisions. In addition to fines and penalties imposed upon violators, some of these state laws also afford private rights of action to individuals who believe their personal information has been misused. For example, California recently enacted legislation, the California Consumer Privacy Act ("CCPA"), that will, among other things, require covered companies to provide new disclosures to California consumers, and afford such consumers new abilities to opt-out of certain sales of personal information, that became effective on January 1, 2020. The CCPA was amended several times throughout 2018 and 2019, and it is unclear whether further modifications will be made to this legislation or how it will be interpreted. In addition, the CCPA requires covered companies to provide new disclosures to individuals and consumers in California, and afford such individuals and consumers new data protection rights, including the ability to opt-out of certain sales of personal information. The GDPR, CCPA and many other laws and regulations relating to privacy and data protection are still being tested in courts, and they are subject to new and differing interpretations by courts and regulatory officials. Additionally, the interplay of federal and state laws may be subject to varying interpretations by courts and government agencies, creating complex compliance issues for us and data we receive, use and share, potentially exposing us to additional expense, adverse publicity and liability. We are working to comply with the GDPR, CCPA and other privacy and data protection laws and regulations that apply to us, and we anticipate needing to devote significant additional resources to complying with these laws and regulations.

It is possible that the GDPR, CCPA or other laws and regulations relating to privacy and data protection may be interpreted and applied in a manner that is inconsistent from jurisdiction to jurisdiction or inconsistent with our current policies and practices and compliance with such laws and regulations could require us to change our business practices and compliance procedures in a manner adverse to our business. We cannot guarantee that we are in compliance with all such applicable data protection laws and regulations and we cannot be sure how these regulations will be interpreted, enforced or applied to our operations. Furthermore, other jurisdictions outside the European Union are similarly introducing or enhancing privacy and data security laws, rules, and regulations, which could increase our compliance costs and the risks associated with noncompliance. It is possible that these laws may be interpreted and applied in a manner that is inconsistent with our practices and our efforts to comply with the evolving data protection rules may be unsuccessful. We cannot guarantee that we or our vendors may be in compliance with all applicable international laws and regulations as they are enforced now or as they evolve. For example, our privacy policies may be insufficient to protect any personal information we collect, or may not comply with applicable laws. Our non-compliance could result in government-imposed fines or orders requiring that we change our practices, which could adversely affect our business. In addition to the risks associated with enforcement activities and potential contractual liabilities, our ongoing efforts to comply with evolving laws and regulations at the federal and state level may be costly and require ongoing modifications to our policies, procedures and systems. In addition, if we are unable to properly protect the privacy and security of protected health information, we could be found to have breached our contracts.

Our actual or perceived failure to adequately comply with applicable laws and regulations relating to privacy and data protection, or to protect personal data and other data we process or maintain, could result in regulatory enforcement actions against us, including fines, imprisonment of company officials and public censure, claims for damages by affected individuals, other lawsuits or reputational and damage, all of which could materially affect our business, financial condition, results of operations and growth prospects.

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 growth prospects.

Our business activities may be subject to the Foreign Corrupt Practices Act and similar anti-bribery and anti-corruption laws, as well as U.S. and certain foreign export controls, trade sanctions, and import laws and regulations.

Our business activities may be subject to the Foreign Corrupt Practices Act of 1977, as amended (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 (the "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.

In addition, in the future once we enter a commercialization phase, our products may be subject to U.S. and foreign export controls, trade sanctions and import laws and regulations. Governmental regulation of the import or export of our products, or our failure to obtain any required import or export authorization for our products, when applicable, could harm our international sales and adversely affect our revenue. Compliance with applicable regulatory requirements regarding the export of our products may create delays in the introduction of our products in international markets or, in some cases, prevent the export of our products to some countries altogether. Furthermore, U.S. export control laws and economic sanctions prohibit the shipment of certain products and services to countries, governments, and persons targeted by U.S. sanctions. If we fail to comply with export and import regulations and such economic sanctions, we may be fined or other penalties could be imposed, including a denial of certain export privileges. Moreover, any new export or import restrictions, new legislation or shifting approaches in the enforcement or scope of existing regulations, or in the countries, persons, or technologies targeted by such regulations, could result in decreased use of our products by, or in our decreased ability to export our products to existing or potential customers with international operations. Any limitation on our ability to export or sell access to our products would likely adversely affect our business.

Inadequate funding for the FDA, the SEC and other government agencies could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of the SEC and other government agencies on which our operations may rely, including those that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable. Disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including from December 22, 2018 until January 25, 2019, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical FDA, SEC and other government employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, in our operations as a public company, future government shutdowns could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations.

Risks Related to Our Reliance on Third Parties

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

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

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

- collaborators generally have significant discretion in determining the efforts and resources that they will apply to these collaborations;

- collaborators may not properly obtain, maintain, enforce, or defend intellectual property or proprietary rights relating to our product candidates or research programs or may use our proprietary information in such a way as to expose us to potential litigation or other intellectual property related proceedings, including proceedings challenging the scope, ownership, validity and enforceability of our intellectual property;

- collaborators may own or co-own intellectual property covering our product candidates or research programs that results from our collaboration with them, and in such cases, we may not have the exclusive right to commercialize such intellectual property or such product candidates or research programs;

- we may need the cooperation of our collaborators to enforce or defend any intellectual property we contribute to or that arises out of our collaborations, which may not be provided to us;

- collaborators may control certain interactions with regulatory authorities, which may impact on our ability to obtain and maintain regulatory approval of our products candidates;

- disputes may arise between the collaborators and us that result in the delay or termination of the research, development, or commercialization of our product candidates or research programs or that result in costly litigation or arbitration that diverts management attention and resources;

- collaborators may decide to not pursue development and commercialization of any product candidates we develop or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborator's strategic focus or available funding or external factors such as an acquisition that diverts resources or creates competing priorities;

- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials, or require a new formulation of a product candidate for clinical testing;

- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates or research programs if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;

- collaborators may restrict us from researching, developing or commercializing certain products or technologies without their involvement;

- collaborators with marketing and distribution rights to one or more product candidates may not commit sufficient resources to the marketing and distribution of such product candidates;
- we may lose certain valuable rights under circumstances identified in our collaborations, including if we undergo a change of control;
- collaborators may grant sublicenses to our technology or product candidates or undergo a change of control and the sublicensees or new owners may decide to take the collaboration in a direction which is not in our best interest;
- collaborators may become bankrupt, which may significantly delay our research or development programs, or may cause us to lose access to valuable technology, know-how or intellectual property of the collaborator relating to our products, product candidates or research programs;
- key personnel at our collaborators may leave, which could negatively impact our ability to productively work with our collaborators;
- collaborations may require us to incur short and long-term expenditures, issue securities that dilute our stockholders, or disrupt our management and business;
- if our collaborators do not satisfy their obligations under our agreements with them, or if they terminate our collaborations with them, we may not be able to develop or commercialize product candidates as planned;
- collaborations may require us to share in development and commercialization costs pursuant to budgets that we do not fully control and our failure to share in such costs could have a detrimental impact on the collaboration or our ability to share in revenue generated under the collaboration;
- collaborations may be terminated in their entirety or with respect to certain product candidates or technologies and, if so terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates or technologies, including our BBB platform technology; and
- collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If a present or future collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our development or commercialization program under such collaboration could be delayed, diminished, or terminated.

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. The failure to develop and commercialize a product candidate pursuant to our agreements with our current or future collaborators could prevent us from receiving future payments under such agreements, which could negatively impact our revenues. 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 time frames. Failure to do so can result in fines, adverse publicity, and civil and criminal sanctions.

Our third-party service providers are not our employees, and we are therefore unable to directly monitor whether or not they devote sufficient time and resources to our clinical and nonclinical programs. These third-party service providers may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other drug development activities that could harm our competitive position. 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, including with the shipment of any drug supplies, could delay clinical development or marketing approval of any product candidates we may develop or commercialization of our medicines, producing additional losses and depriving us of potential product revenue.

We contract with third parties for the manufacture of materials for our research programs and preclinical studies and expect to continue to do so for clinical trials and for commercialization of any product candidates that we may develop. This reliance on third parties 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 growth 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, programs and product candidates, as well as other technologies that are important to our business. Given that the development of our technology and product candidates is at an early stage, our intellectual property portfolio with respect to certain aspects of our technology and product candidates is also at an early stage. For example, as of December 31, 2019, we do not own or in-license any issued patents in the United States directed to the composition of matter of any of the antibodies or enzymes that we have thus far developed using our BBB platform technology. In addition, we do not own or in-license any issued United States patents covering the composition of matter of the Fc domain portion of our BBB platform technology that binds to transferrin receptor, or any issued United States patents that cover the composition of matter of antibodies or enzymes being developed in our TREM2, aSyn, Tau or IDS programs. We have filed or intend to file patent applications on these aspects of our technology and 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, 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, 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, programs and product candidates could have a material adverse effect on our business, financial condition, results of operations and growth 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 nondisclosure 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 growth 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 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. If we or our collaborators are unsuccessful in any such proceeding or other priority or inventorship dispute, we may be required to obtain and maintain licenses from third parties, including parties involved in any such interference proceedings or other priority or inventorship disputes. Such licenses may not be available on commercially reasonable terms or at all, or may be non-exclusive. If we are unable to obtain and maintain such licenses, we may need to cease the development, manufacture, and commercialization of one or more of the product candidates we may develop. The loss of exclusivity or the narrowing of our owned and licensed patent claims could limit our ability to stop others from using or commercializing similar or identical technology and products.

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. 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 growth 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 or licenses granted by us to others.

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

Our agreements with F-star and other license agreements may not provide exclusive rights to use certain licensed intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology and products in the future. For example, F-star retains the right to use itself, and to license to others, its modular antibody technology for any purpose other than the targets 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. Also, under our agreement with Sanofi, they control prosecution, and in specified circumstances, enforcement of certain of the patents and patent applications licensed to them. We cannot be certain that our in-licensed or out-licensed patents and patent applications that are controlled by our licensors or licensees will be prepared, filed, prosecuted, maintained, enforced, and defended in a manner consistent with the best interests of our business. If our licensors or licensees 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 growth 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 growth 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 growth 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 growth 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 growth 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 growth 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 growth 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 (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 growth 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 or raise a defense to infringement. 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 subject matter eligibility for patenting, 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. Grounds for defenses to infringement include statutory exemptions to patent infringement for uses related to submitting information to regulatory authorities to seek certain regulatory approvals. 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, a judge or jury could find that our patent claims laws of nature or are otherwise ineligible for patenting, and 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 growth 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 growth 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 growth 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 nondisclosure 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 growth 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 growth 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 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 or growth prospects.

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 in which we have an interest 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 growth 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 growth 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 December 31, 2019, we had 261 employees, all of whom were full-time. As our development plans and strategies develop, 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.

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

We have in the past engaged in acquisitions and strategic partnerships, and we may engage in various acquisitions and strategic partnerships in the future, including licensing or acquiring complementary products, intellectual property rights, technologies, or businesses. For instance, in January 2018 we entered into the Takeda Collaboration Agreement, as amended in February 2019, and in connection therewith we issued and sold to Takeda 4,214,559 shares of our common stock for an aggregate purchase price of $110.0 million in February 2018. On May 30, 2018, we exercised our buy-out option in connection with the F-star Collaboration Agreement and entered into a Purchase Agreement pursuant to which we acquired all of the outstanding shares of F-star Gamma. Further, on October 29, 2018, we entered into the Sanofi Collaboration Agreement. 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 other breakdowns, cyberattacks or information security breaches that could compromise the confidentiality, integrity, and availability of such systems and data, expose us to liability, and affect our reputation.

We are increasingly dependent upon information technology systems, infrastructure, and data to operate our business. We also rely on third party vendors and their information technology systems. Despite the implementation of security measures, our internal computer systems and those of our CROs and other contractors and consultants may be vulnerable to damage from computer viruses or unauthorized access, or breached due to operator error, malfeasance or other system disruptions. As the cyber-threat landscape evolves, these attacks are growing in frequency, sophistication and intensity, and are becoming increasingly difficult to detect. These threats can come from a variety of sources, ranging in sophistication from an individual hacker to a state-sponsored attack. Cyber threats may be generic, or they may be custom-crafted against our information systems. Over the past few years, cyber-attacks have become more prevalent, intense, sophisticated and much harder to detect and defend against. Such attacks could include the use of key loggers or other harmful and virulent malware, including ransomware or other denials of service, and can be deployed through malicious websites, the use of social engineering and/or other means. We and our third party vendors may not be able to anticipate all types of security threats, and we may not be able to implement preventive measures effective against all such security threats. The techniques used by cyber criminals change frequently, may not be recognized until launched, and can originate from a wide variety of sources. Although to our knowledge we and our vendors have not experienced any such material system failure or security breach to date, if a breakdown, cyberattack or other information security breach were to occur and cause interruptions in our operations, it could result in a material disruption of our development programs and our business operations , whether due to a loss of trade secrets or other proprietary information or other similar disruption and we could incur liability and reputational damage. 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.

Cyber-attacks, breaches, interruptions or other data security incidents could result in legal claims or proceedings, liability under federal or state laws that protect the privacy of personal information, regulatory penal-ties, significant remediation costs, disrupt key business operations and divert attention of management and key information technology resources. In the United States, notice of breaches must be made to affected individuals, the U.S. Secretary of the Department of Health and Human Services ("HHS"), and for extensive breaches, notice may need to be made to the media or U.S. state attorneys general. Such a notice could harm our reputation and our ability to compete. The HHS has the discretion to impose penalties without attempting to resolve violations through informal means. In addition, U.S. state attorneys general are authorized to bring civil actions seeking either injunctions or damages in response to violations that threaten the privacy of state residents. There can be no assurance that we, our collaborators, CROs, vendors, and any other business counterparties will be successful in efforts to detect, prevent, protect against or fully recover systems or data from all break-downs, service interruptions, attacks or breaches of systems. In addition, we do not maintain standalone cyber-security insurance and have limited insurance coverage in the event of any breach or disruption of our or our collaborators', CROs', or vendors' systems, including any unauthorized access or loss of any personal data that we may collect, store or otherwise process. The costs related to significant security breaches or disruptions could be material and exceed the limits of any insurance coverage we may have. 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, including data related to our personnel, we could incur liability and the further development and commercialization of our product candidates could be delayed and our business and operations could be adversely affected and/or could result in the loss or disclosure of critical or sensitive data, which could result in financial, legal, business or reputational harm to us.

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, CDMOs, 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 such as Coronavirus, 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, UK Bribery Act or comparable foreign laws;
- business interruptions resulting from geo-political actions, including war and terrorism, natural disasters including earthquakes, typhoons, floods and fires, or health epidemics such as Coronavirus; and
- cyberattacks, which are growing in frequency, sophistication and intensity, and are becoming increasingly difficult to detect.

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, 2019, we had federal net operating loss carryforwards of approximately $221.5 million, federal research and development tax credit carryforwards of approximately $14.5 million, and orphan tax credit carryforwards of approximately $1.7 million which will begin to expire in 2035. Under Sections 382 and 383 of the United States Internal Revenue Code of 1986, as amended, (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 IPO in December 2017 and private placements and other transactions that have occurred since our incorporation, we may have experienced such an ownership change. We may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which are outside our control. As a result, our ability to use our pre-change net operating loss carryforwards and other pre-change tax attributes to offset post-change taxable income or taxes may be subject to limitation.

We may be subject to adverse legislative or regulatory tax changes that could negatively impact our financial condition.

The rules dealing with U.S. federal, state and local income taxation are constantly under review by persons involved in the legislative process and by the IRS and the U.S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect our stockholders or us. In recent years, many such changes have been made and changes are likely to continue to occur in the future. For example, in December 2017, Congress passed the Tax Cuts and Jobs Act, which made broad and complex changes to the tax laws. We cannot predict whether, when, in what form, or with what effective dates, tax laws, regulations and rulings may be enacted, promulgated or decided, which could result in an increase in our, or our stockholders’, tax liability or require changes in the manner in which we operate in order to minimize increases in our tax liability.

Future changes to the tax laws relating to multinational corporations could adversely affect us.

Under current law, we are treated as a foreign corporation for U.S. federal tax purposes. However, changes to the U.S. Internal Revenue Code, U.S. Treasury Regulations or other IRS guidance thereunder could adversely affect our status as a foreign corporation or otherwise affect our effective tax rate. In addition, the U.S. Congress, the IRS, the Organization for Economic Co-operation and Development and other governments and agencies in jurisdictions where we do business have recently focused on issues related to the taxation of multinational corporations, and specifically in the area of “base erosion and profit shifting,” where payments are made between affiliates from a jurisdiction with high tax rates to a jurisdiction with lower tax rates. As a result, the tax laws in the U.S. and other countries in which we do business could change on a prospective or retroactive basis, and any such changes could have an adverse effect on our business, financial condition, results of operations or growth prospects.

Risks Related to Ownership of Our Common Stock

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

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

- the success of existing or new competitive products or technologies;

- the timing and results of clinical trials for our current product candidates and any future product candidates that we may develop;
- commencement or termination of collaborations for our product development and research programs;
- failure to achieve development, regulatory or commercialization milestones under our collaborations;
- failure or discontinuation of any of our product development and research programs;
- failure to develop our BBB platform technology;
- results of preclinical studies, clinical trials, or regulatory approvals of product candidates of our competitors, or announcements about new research programs or product candidates of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents, or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our research programs, clinical development programs, or product candidates that we may develop;
- the results of our efforts to develop additional product candidates or products;
- 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;
- 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;
- adoption of new accounting standards or changes in accounting standards;
- ineffectiveness of our internal controls;
- significant lawsuits, including patent or stockholder litigation;
- market conditions in the pharmaceutical and biotechnology sectors; and
- general economic, industry, and market conditions.

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

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

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

Sales of substantial amounts of our common stock in the public markets, or the perception that such sales might occur, 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 or the perception that these sales might occur, could depress the market price of our common stock and could impair our ability to raise capital through the sale of additional equity securities. We are unable to predict the effect that sales may have on the prevailing market price of our common stock.

Sales of our common stock by current stockholders may make it more difficult for us to sell equity or equity-related securities in the future at a time and price that we deem reasonable or appropriate, and make it more difficult for you to sell shares of our common stock.

Certain holders of shares of our common stock 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. Registration of these shares under the Securities Act would result in the shares becoming freely tradeable in the public market, subject to the restrictions of Rule 144 in the case of our affiliates. Any sales of securities by these stockholders could have a material adverse effect on the market price for our common stock.

We have registered on Form S-8 all shares of common stock that are issuable under our 2017 Equity Incentive Plan and 2017 Employee Stock Purchase Plan. As a consequence, these shares can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates.

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. On March 12, 2019, we filed a shelf registration statement on Form S-3 (File No. 333-230232) with the Securities and Exchange Commission, which became effective upon filing. The shelf registration allows us to sell, from time to time, an unspecified number of shares of common stock; shares of preferred stock; debt securities; warrants to purchase shares of common stock, preferred stock, or other securities; purchase contracts; and units representing two or more of the foregoing securities. Additionally, any future collaborations we enter into with third parties may provide capital in the near term but limit our potential cash flow and revenue in the future. If we raise additional funds through strategic partnerships and alliances and licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies or product candidates, or grant licenses on terms unfavorable to us.

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

As of December 31, 2019, our directors, executive officers, holders of more than 5% of our outstanding stock and their respective affiliates beneficially own shares representing more than 50.0% of our outstanding common stock. As a result, these stockholders, if they act together, may significantly influence all matters requiring stockholder approval, including the election of directors and approval of significant corporate transactions. This concentration of ownership may have the effect of delaying or preventing a change in control of our company that our other stockholders may believe is in their best interests. This in turn could have a material adverse effect on our stock price and may prevent attempts by our stockholders to replace or remove the board of directors or management.

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

As a public company, we are subject to reporting and other obligations under the Securities Exchange Act of 1934, as amended, (the "Exchange Act"), including the requirements of Section 404 of the Sarbanes-Oxley Act, which require annual management assessments of the effectiveness of our internal control over financial reporting.

The rules governing the standards that must be met for management and our auditors 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 or auditors may identify material weaknesses or deficiencies which may not be remedied in time to meet the deadline imposed by the Sarbanes-Oxley Act. 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 ("U.S. GAAP"). Any failure to maintain effective internal controls could have an adverse effect on our business, financial position, results of operations and growth prospects.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

We are subject to the periodic reporting requirements of the Exchange Act. We designed our disclosure controls and procedures to reasonably assure that information we must disclose in reports we file or submit under the Exchange Act is accumulated and communicated to management, and recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well-conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met.

These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements due to error or fraud may occur and not be detected.

We have not paid and do not expect to pay any dividends for the foreseeable future. Any return on investment may be limited to the value of our common stock. Investors may never obtain a return on their investment.

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

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

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

- establish that our board of directors is divided into three classes, Class I, Class II and Class III, with each class serving staggered three-year terms;
- provide that vacancies on our board of directors may be filled only by a majority of directors then in office, even though less than a quorum;
- provide that our directors may only be removed for cause;
- eliminate cumulative voting in the election of directors;
- authorize our board of directors to 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, (the "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, 15.0% of our voting stock, for a period of three years after the date of the transaction in which the person became an interested stockholder, unless the business combination is approved in a prescribed manner.

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

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

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

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

Our amended and restated certificate of incorporation further provides that the federal district courts of the United States of America will be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act (such provision, the "Federal Forum Provision"). However, as previously disclosed in our Current Report on Form 8-K filed with the SEC on January 4, 2019, in light of the decision issued by the Delaware Court of Chancery in Matthew Sciabacucchi v. Matthew B. Salzberg et al., C.A. No. 2017-0931-JTL (Del. Ch.), finding that provisions such as the Federal Forum Provision are not valid under Delaware law, we do not intend to enforce the Federal Forum Provision unless and until such time that Court of Chancery, or the Delaware Supreme Court, determines that such a provision is valid under Delaware law.

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 or we do not enforce such provision, we may incur additional costs associated with resolving the dispute in other jurisdictions, which could seriously harm our business.

ITEM 1B. UNRESOLVED STAFF COMMENTS

None.

ITEM 2. PROPERTIES

Our corporate headquarters are located in South San Francisco, California, comprising 148,020 square feet of office, research and development, engineering and laboratory space pursuant to a lease agreement which commenced on April 12, 2019 and expires on April 30, 2029, with an option to extend for a period of ten years. This facility houses all our personnel. We believe that our existing premises are adequate for our current needs.

ITEM 3. LEGAL PROCEEDINGS

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

ITEM 4. MINE SAFETY DISCLOSURES

Not applicable.

PART II

ITEM 5. MARKET FOR REGISTRANT'S COMMON EQUITY, RELATED STOCKHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Our common stock has been listed on The NASDAQ Global Select Market under the symbol "DNLI" since December 8, 2017. Prior to that date, there was no public trading market for our common stock.

Holders of Common Stock

As of February 19, 2020, there were 35 holders of record of our common stock. The actual number of stockholders is greater than this number of record holders and includes stockholders who are beneficial owners but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust or by other entities.

Dividend Policy

We have never declared or paid any cash dividends on our common stock or any other securities. We anticipate that we will retain all available funds and any future earnings, if any, for use in the operation of our business and do not anticipate paying cash dividends in the foreseeable future. In addition, future debt instruments may materially restrict our ability to pay dividends on our common stock. Payment of future cash dividends, if any, will be at the discretion of the board of directors after taking into account various factors, including our financial condition, operating results, current and anticipated cash needs, the requirements of current or then-existing debt instruments and other factors the board of directors deems relevant.

Performance Graph

This graph is not "soliciting material" or deemed "filed" with the SEC for purposes of Section 18 of the Exchange Act, or otherwise subject to liabilities under that Section, and shall not be deemed incorporated by reference into any filing of Denali Therapeutics Inc. under the Securities Act of 1933, as amended (the "Securities Act"), whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.

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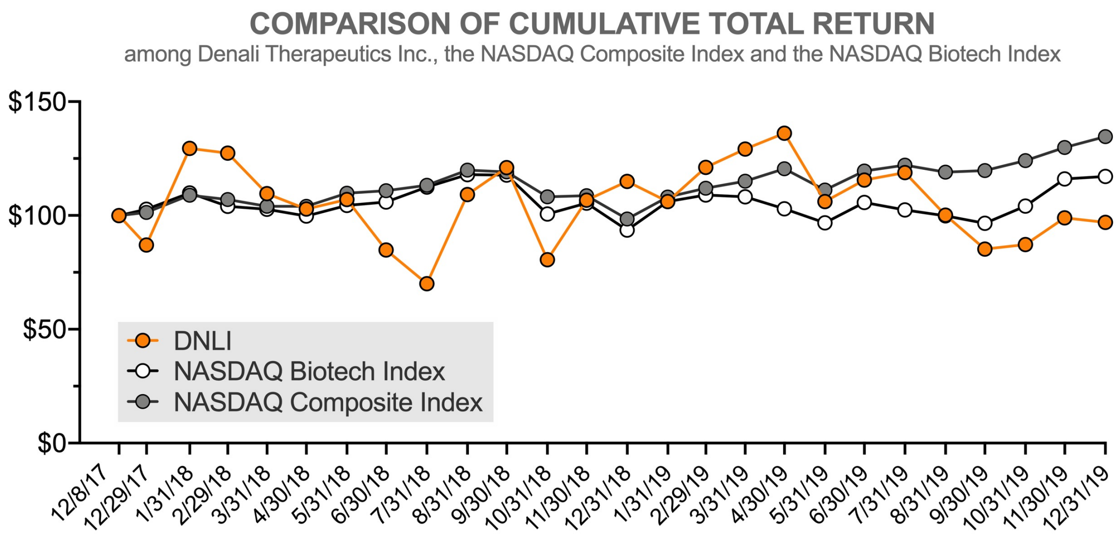
The following graph compares the cumulative total return to stockholder return on our common stock relative to the cumulative total returns of the NASDAQ Composite Index and the NASDAQ Biotechnology Index. An investment of $100 is assumed to have been made in our common stock and each index on December 8, 2017 (the first day of trading of our common stock) and its relative performance is tracked through December 31, 2019. Pursuant to applicable Securities and Exchange Commission rules, all values assume reinvestment of the full amount of all dividends, however no dividends have been declared on our common stock to date. The stockholder returns shown on the graph below are based on historical results and are not necessarily indicative of future performance, and we do not make or endorse any predictions as to future stockholder returns.



	12/8/17	12/31/17	3/31/18	6/30/18	9/30/18	12/31/18	3/31/19	6/30/19	9/30/19	12/31/19
Denali Therapeutics Inc.	$ 100.00	$ 87.03	$ 109.57	$ 84.66	$ 120.98	$ 114.97	$ 129.22	$ 115.53	$ 85.25	$ 96.94
NASDAQ Composite Index	100.00	101.37	103.99	110.87	119.09	98.49	115.04	119.50	119.71	134.63
NASDAQ Biotechnology Index	100.00	102.71	102.77	105.93	117.79	93.61	108.16	105.72	96.61	117.11

Recent Sales of Unregistered Securities

There were no sales of unregistered securities during the period covered by this Annual Report on Form 10-K, other than those previously reported in a Quarterly Report on Form 10-Q or in a Current Report on Form 8-K.

Use of Proceeds from Registered Securities

On December 7, 2017, our Registration Statement on Form S-1 (File No. 333-221522) was declared effective by the SEC for our initial public offering of common stock. We started trading on The NASDAQ Global Select Market on December 8, 2017, and the transaction formally closed on December 12, 2017. In connection with the initial public offering, we sold an aggregate of 15,972,221 shares of common stock, including 2,083,333 shares sold pursuant to the underwriters' full exercise of their option to purchase additional shares, at a price to the public of $18.00 per share. The aggregate offering price for shares sold in the offering was $287.5 million. The joint book-running managers for the initial public offering were Goldman, Sachs & Co. LLC, Morgan Stanley & Co. LLC, and J.P. Morgan Securities LLC. After deducting underwriting discounts, commissions and offering expenses paid or payable by us of approximately $23.2 million, the net proceeds from the offering were approximately $264.3 million. No offering expenses were paid or are payable, directly or indirectly, to our directors or officers, to persons owning 10.0% or more of any class of our equity securities or to any of our affiliates. There has been no material change in the planned use of proceeds from our initial public offering as described in our final prospectus filed with the SEC on December 8, 2017 pursuant to Rule 424(b)(4). We invested the funds received in short-term, interest-bearing investment-grade securities and government securities.

In January 2020, we sold 9.0 million shares of common stock (inclusive of shares sold pursuant to an overallotment option granted to the underwriters in connection with the offering) through an underwritten public offering at a price of $23.00 per share for aggregate net proceeds of approximately $194.1 million. There has been no material change in the planned use of the net proceeds from the follow-on public offering as described in the Registration Statement. We invested the funds received in short-term, interest-bearing investment-grade securities and government securities.

Issuer Purchases of Equity Securities

Not applicable.

ITEM 6. SELECTED FINANCIAL DATA

The following tables summarize our selected consolidated financial data for the periods and as of the dates indicated. We derived the consolidated financial data for the years ended December 31, 2019, 2018, and 2017 and as of December 31, 2019 and 2018 from our audited consolidated financial statements and related notes included elsewhere in this report. We derived the consolidated financial data for the years ended December 31, 2016 and 2015 and as of December 31, 2017, 2016 and 2015 from our audited consolidated financial statements that are not included elsewhere in this report.

Our historical results are not necessarily indicative of the results that may be expected in the future. 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 report.

	Year Ended December 31,				
	2019	2018	2017	2016	2015
	(In thousands, except share and per share amounts)				
Consolidated Statements of Operations and Comprehensive Loss Data:					
Collaboration revenue	$ 26,678	$ 129,160	$ —	$ —	$ —
Operating expenses:					
Research and development	193,382	143,183	74,460	75,702	11,571
General and administrative	46,480	32,349	15,680	11,731	5,108
Total operating expenses	239,862	175,532	90,140	87,433	16,679
Loss from operations	(213,184)	(46,372)	(90,140)	(87,433)	(16,679)
Interest and other income (expense), net	15,219	10,132	1,955	781	(109)
Loss before income taxes	(197,965)	(36,240)	(88,185)	(86,652)	(16,788)
Income tax benefit	351	—	—	—	—
Net loss	(197,614)	(36,240)	(88,185)	(86,652)	(16,788)
Other comprehensive income (loss):	999	(281)	5	(373)	—
Comprehensive loss	$ (196,615)	$ (36,521)	$ (88,180)	$ (87,025)	$ (16,788)
Net loss per share, basic and diluted	$ (2.07)	$ (0.39)	$ (5.89)	$ (13.49)	$ (5.58)
Weighted average number of shares outstanding, basic and diluted	95,608,208	92,621,991	14,964,144	6,424,720	3,006,379

	As of December 31,				
	2019	2018	2017	2016	2015
Consolidated Balance Sheet Data:					
Cash, cash equivalents and marketable securities	$ 455,242	$ 612,178	$ 466,976	$ 250,911	$ 30,740
Working capital(1)	384,687	448,050	395,443	172,849	29,950
Total assets	553,231	661,984	486,721	271,067	36,683
Total liabilities	158,341	115,139	20,925	16,548	4,009
Convertible preferred stock	—	—	—	348,673	48,308
Accumulated deficit	(425,551)	(227,937)	(191,697)	(103,512)	(16,860)
Total stockholders' equity (deficit)	$ 394,890	$ 546,845	$ 465,796	$ (94,154)	$ (15,634)

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

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

The following discussion and analysis of our financial condition and results of operations should be read together with the section titled "Selected Financial and Other Data" and our consolidated financial statements and the related notes to those statements included elsewhere in this report. This discussion and analysis and other parts of this report 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 report.

Overview

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

Our strategy is guided by three overarching principles that we believe 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 select our therapeutic targets and disease pathways based on genes that, when mutated, cause, or are major risk factors for, neurodegenerative diseases. We refer to these genes as degenogenes;

- **Engineering Brain Delivery**: We engineer our product candidates to cross the blood-brain barrier and act directly in the brain; and

- **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 are developing a broad portfolio of targeted therapeutic candidates for neurodegenerative diseases. Our programs are at different stages of clinical and preclinical development, including five programs in clinical studies.

We have also developed a proprietary blood-brain barrier ("BBB") platform technology, our transport vehicle ("TV"), which enables multiple modality-based platforms to deliver a wide range of large-molecule therapeutics across the BBB, including enzymes, antibodies, proteins and oligonucleotides. This technology is designed to engage specific BBB transport receptors, which are ubiquitously expressed in brain capillaries and facilitate transport of proteins into the brain. We are currently optimizing and broadening this platform technology.

Our five clinical programs are:

- our leucine-rich repeat kinase 2 ("LRRK2") inhibitor program to address Parkinson's disease;

- our receptor interacting serine/threonine protein kinase 1 ("RIPK1") inhibitor program, partnered with Sanofi, to address neurological diseases such as Alzheimer's disease and amyotrophic lateral sclerosis ("ALS");

- a second RIPK1 inhibitor that our partner Sanofi is developing to address peripheral inflammatory diseases such as rheumatoid arthritis;

- our EIF2B activator program to address diseases such as ALS and FTD; and

- our ETV:IDS program, our most advanced program enabled by our TV technology, which is designed to restore iduronate 2-sulfatase ("IDS"), and reduce glycosaminoglycans ("GAGs"), both peripherally and in the brain, in patients with mucopolysaccharidosis II ("MPS II", or "Hunter syndrome").

The following table summarizes key information about our clinical stage programs:

Program	Product Candidate(s)	Clinical Phase	Indication(s)	Operational Control
LRRK2	DNL201	Ph 1b (complete)	Parkinson's disease	Denali
	DNL151	Ph 1 and Ph 1b		
RIPK1 (CNS)	DNL747	Ph 1b	Alzheimer's disease	Denali
		Ph 1b	ALS	Sanofi
RIPK1 (Peripheral)	DNL758	Ph 1	Systemic inflammatory diseases	Sanofi
EIF2B	DNL343	Ph 1	ALS and FTD	Denali
ETV:IDS	DNL310	Ph 1 (study startup)	Hunter syndrome	Denali

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, 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 understanding key neurodegenerative disease pathways.

Key operational and financing milestones for the year ended December 31, 2019 and in 2020 to date include:

- In February 2019, we received a payment of $5.0 million related to a preclinical milestone earned in December 2018 under the Takeda Collaboration Agreement;

- In January 2019, we announced, in collaboration with our partner Sanofi, the first patient dosed in our Phase 1b study of DNL747 in ALS patients, and in February 2019, we announced the first patient dosed in our Phase 1b study of DNL747 in Alzheimer's disease patients;

- In February 2019, DNL310 (ETV:IDS) was granted orphan drug designation and rare pediatric disease designation by the FDA;

- In April 2019, we completed our move to our new headquarters location;

- In July 2019, our partner Sanofi commenced dosing of our partnered small molecule RIPK1 inhibitor, DNL758, in a Phase 1 clinical study in healthy volunteers. This triggered a milestone payment of $10.0 million, which was received in August 2019;

- In September 2019, we announced the first patient dosed in our Phase 1b study of DNL151 in patients with Parkinson's disease, and the launch of our Engage Parkinson's website;

- In October 2019, we enrolled the first patient in a biomarker study for our ETV:IDS program in Hunter Syndrome. This non-interventional study is expected to yield critical biomarker and clinical data in patients to inform future clinical studies with DNL310 (ETV:IDS) and facilitate patient recruitment into these studies;

- In November 2019, we announced progress of our DNL747 Phase 1b trials in Alzheimer's disease and ALS, commencement of enrollment of an ALS open label extension in the Netherlands and expansion of sites for the Phase 1b ALS study into the United States. We intend, together with our partner Sanofi, to evaluate the full data set from the ongoing clinical and preclinical studies to inform decisions on further clinical testing for our RIPK1 program. The timing of such decisions is mid-2020;

- In January 2020, the IND for DNL310 (ETV:IDS) was accepted. We plan to initiate a Phase 1/2 study for DNL310 in Hunter syndrome patients in the first half of 2020.

- In January 2020, we announced positive results from our LRRK2 program. Phase 1b results with DNL201 in patients with Parkinson’s disease demonstrated high levels of target and pathway engagement and improvement of lysosomal biomarkers. Phase 1 results with DNL151 in more than 150 healthy volunteers also met all safety and biomarker goals. We plan to select one of these two molecules for Phase 2/3 studies in patients with and without the LRRK2 mutation in mid-2020.

- In January 2020, we sold 9.0 million shares of common stock (inclusive of shares sold pursuant to an overallotment option granted to the underwriters in connection with the offering) through an underwritten public offering at a price of $23.00 per share for aggregate net proceeds of approximately $194.1 million.

- In February 2020, we initiated a Phase 1 clinical trial for DNL343 in healthy volunteers.

We do not have any products approved for sale and have not generated any product revenue since our inception. We have funded our operations primarily from the issuance and sale of convertible preferred stock, the proceeds from our IPO and our follow on offering, and payments received from our collaboration agreements with Takeda and Sanofi.

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 $197.6 million, $36.2 million and $88.2 million for the years ended December 31, 2019, 2018 and 2017, respectively. As of December 31, 2019, we had an accumulated deficit of $425.6 million. We expect to continue to incur significant expenses and operating losses as we advance our current clinical stage programs through healthy volunteer and patient 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.

License and Collaboration Agreements

Takeda

In January 2018, we entered into the Collaboration Agreement with Takeda (“Takeda Collaboration Agreement”) pursuant to which we granted Takeda an option with respect to three of our programs to develop and commercialize, jointly with us, certain biologic products that are enabled by our BBB delivery technology and intended for the treatment of neurodegenerative disorders. The three programs were Denali’s ATV:BACE1/Tau, ATV:TREM2 and PTV:PGRN programs. The Takeda Collaboration Agreement became effective in February 2018 when the requirements of the Hart-Scott-Rodino Antitrust Improvements Act of 1976 ("HSR") were satisfied. In February 2019, we amended the Takeda Collaboration Agreement to replace the ATV:BACE1/Tau program with the ATV:Tau program.

Under the terms of the Takeda Collaboration Agreement, Takeda paid us a $40.0 million upfront payment, and is obligated to pay us up to an aggregate of $25.0 million with respect to each program under the Takeda Collaboration Agreement directed to a target and based upon the achievement of certain preclinical milestone events, up to $75.0 million in total, of which we have earned and received $15.0 million to date. Takeda is also obligated to pay us a $5.0 million option fee for each target for which Takeda exercises its option, up to $15.0 million in total.

Pursuant to the terms of the Takeda Collaboration Agreement, we entered into the Purchase Agreement with Takeda in January 2018, pursuant to which we agreed to issue and sell, and Takeda agreed to purchase, 4,214,559 shares of our common stock for an aggregate purchase price of $110.0 million. We closed the sale of the 4,214,559 shares of our common stock to Takeda on February 23, 2018.

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

In addition, if Takeda exercises its option for all three collaboration programs, Takeda may be obligated to pay us up to an aggregate of $407.5 million upon achievement of certain clinical milestone events and up to an aggregate of $300.0 million in regulatory milestone events relating to receipt of regulatory approval in the United States, certain European countries and Japan. Takeda may also be obligated to pay us up to $75.0 million per biologic product upon achievement of a certain sales-based milestone, or an aggregate of $225.0 million if one biologic product from each program achieves this milestone.

We have recognized collaboration revenue of $5.9 million and $5.7 million associated with the Takeda Collaboration Agreement in the years ended December 31, 2019 and 2018, respectively, and recorded a receivable from Takeda of $5.0 million on the consolidated balance sheet as of December 31, 2018. We did not have a receivable from Takeda as of December 31, 2019. Through December 31, 2019, we have received $15.0 million in preclinical milestone payments from Takeda and have not recorded any product sales under the Takeda Collaboration Agreement.

Sanofi

In October 2018, we entered into the Sanofi Collaboration Agreement with Sanofi pursuant to which certain small molecule CNS and peripheral RIPK1 inhibitors contributed by Sanofi and by Denali will be developed and commercialized. The Sanofi Collaboration Agreement became effective in November 2018 when the HSR requirements were satisfied. Under the terms of the Collaboration Agreement, Sanofi paid us a $125.0 million upfront payment. Under the Sanofi Collaboration Agreement, Sanofi is required to make milestone payments up to approximately $1.1 billion upon achievement of certain clinical, regulatory and sales milestone events. Such milestone payments include $215.0 million in clinical milestone payments and $385.0 million in regulatory milestone payments for CNS Products, as defined, that are developed and approved in the United States, by the European Medicines Agency ("EMA") and in Japan for three indications, including Alzheimer's disease. These milestones also include $120.0 million in clinical milestone payments, $175.0 million in regulatory milestone payments and $200.0 million in commercial milestone payments for Peripheral Products, as defined, that are developed and approved in the United States, by the EMA and in Japan for three indications. Through December 31, 2019, we have received milestone payments of $10.0 million under the Sanofi Collaboration Agreement.

Denali will share profits and losses equally with Sanofi for CNS Products sold in the United States and China, and receive royalties on net sales for CNS Products outside of the United States and China and for Peripheral Products sold worldwide, each as further described below. RIPK1 Inhibitors contributed by Sanofi and developed and commercialized under the Sanofi Collaboration Agreement will be subject to lower milestone and royalty payments to us compared to RIPK1 Inhibitors contributed by us. We will also retain responsibility for certain payment obligations under our agreement with an academic institution which licensed certain intellectual property to us that we are sublicensing to Sanofi under the Sanofi Collaboration Agreement.

Denali and Sanofi will jointly develop CNS Products pursuant to a global development plan. We will be responsible, at our cost, for the conduct of Phase 1 and Phase 2 trials for CNS Products for Alzheimer’s disease and any activities required to support such clinical trials and specific for Alzheimer’s disease. We will also conduct, at Sanofi’s cost, a Phase 1b trial for DNL747 for ALS. Sanofi will be responsible, at its cost, for all other Phase 1 and Phase 2 trials for CNS Products, including for multiple sclerosis. Sanofi will lead the conduct of all Phase 3 and later stage development trials for CNS Products, with Sanofi funding 70% of such costs and Denali funding 30% of such costs. We have the ability to opt out of the cost-profit sharing provisions of the Sanofi Collaboration Agreement, as further described below.

Sanofi will lead commercialization activities globally for CNS Products. We may elect to conduct certain co-commercialization activities outside of MS with respect to each CNS Product in the United States and/or China, provided that the cost-profit sharing provisions of the Sanofi Collaboration Agreement for the relevant CNS Product are still in effect, as further described below.

We may opt out of the cost-profit sharing provisions of the Sanofi Collaboration Agreement for CNS Products in the United States and China on a CNS Product-by-CNS Product and country-by-country basis. Sanofi may also terminate our cost-profit sharing provisions of the Sanofi Collaboration Agreement in its entirety if, following notice from Sanofi and a cure period, we fail to satisfy our cost-sharing obligations. After such an opt out by us or termination by Sanofi, we will no longer be obligated to share in the development and commercialization costs for the applicable CNS Products and we will not share in the applicable profits from such CNS Products. Instead, we will be entitled to receive tiered royalties on net sales of the applicable CNS Products in the relevant country (or countries). The royalty rates will be a percentage in the low double digits to mid-teens, but may increase to the mid-teens to low-twenties percentages for all countries in which Sanofi is paying royalties on the applicable CNS products, if we have met certain co-funding thresholds at the time of our election or Sanofi's termination of our cost-profit sharing rights and obligations.

Sanofi will be responsible, at its cost, for conducting activities relating to the development and commercialization of all Peripheral Products. Sanofi will lead commercialization activities globally for Peripheral Products. We will be entitled to receive tiered royalties in the low- to mid- teen percentages on net sales of Peripheral Products.

We have recognized collaboration revenue of $20.8 million and $123.5 million associated with the Sanofi Collaboration Agreement in the years ended December 31, 2019 and 2018, respectively, and recorded a receivable from Sanofi of $1.2 million and $2.3 million on the consolidated balance sheet as of December 31, 2019 and 2018, respectively. Through December 31, 2019, we have received milestone payments of $10.0 million and have not recorded any product sales under the Sanofi Collaboration Agreement.

F-star

In August 2016, we entered into a License and Collaboration Agreement ("F-star Collaboration Agreement") with F-star Gamma Limited ("F-star Gamma"), F-star Biotechnologische Forschungs-Und Entwicklungsges m.b.H ("F-star GmbH") and F-star Biotechnology Limited ("F-star Ltd") (collectively, "F-star"). 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. 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, 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 ("Option Agreement").

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

As a result of the Acquisition, F-star Gamma became our wholly-owned subsidiary and the entity's name was changed to Denali BBB Holding Limited. In addition, we became a direct licensee of certain intellectual property of F-star Ltd by way of our assumption of F-star Gamma’s license agreement with F-star Ltd, dated August 24, 2016, (the “F-star Gamma License”). We made initial exercise payments of $18.0 million in aggregate under the Purchase Agreement and the F-star Gamma License, less the net liabilities of F-star Gamma, which were approximately $0.2 million. In addition, we are required to make future contingent payments, to F-star Ltd and the former shareholders of F-star Gamma, up to a maximum amount of $447.0 million in the aggregate upon the achievement of certain defined preclinical, clinical, regulatory and commercial milestones. These include up to $27.0 million in preclinical contingent payments, $50.0 million in clinical contingent payments, $120.0 million in regulatory contingent payments and $250.0 million in commercial contingent payments. The amount of the contingent payments will vary based on whether F-star delivers an Fcab (constant Fc-domains with antigen-binding activity) that meets pre-defined criteria and whether the Fcab has been identified solely by us or solely by F-star Ltd. or jointly by us and F-star Ltd. In June 2019, we made a payment of $1.5 million to F-star Ltd upon the achievement of a specified preclinical milestone in our ETV:IDS program.

Under the terms of the original F-star Collaboration Agreement, we could nominate up to three Fcab targets (“Accepted Fcab Targets”) within the first three years of the date of the F-star Collaboration Agreement. Upon entering into the F-star Collaboration Agreement, we selected transferrin receptor (“TfR”) as the first Accepted Fcab Target and paid F-star Gamma an upfront fee of $5.5 million, which included selection of the first Accepted Fcab Target. In May 2018, we exercised its right to nominate two additional Fcab Targets and identified a second Accepted Fcab Target. We are obligated to make a one-time payment for the two additional Accepted Fcab Targets of $6.0 million in the aggregate and have extended the time period for our selection of the third Accepted Fcab Target until approximately the fourth anniversary of the date of the original F-star Collaboration Agreement, or August 2020.

We recognized $1.5 million and $18.3 million of contingent consideration as research and development expense in the years ended December 31, 2019 and 2018, respectively. A further $6.0 million for the nomination of two additional Accepted Fcab Targets under the F-star Collaboration Agreement was recognized as research and development expense in the year ended December 31, 2018, along with the upfront option fee of $0.5 million previously included within other non-current assets. We recognized an additional $1.1 million, $0.8 million and $1.1 million of research and development expense related to the funding of F-star research costs for the years ended December 31, 2019, 2018 and 2017, respectively.

Genentech

In June 2016, we entered into an Exclusive License Agreement with Genentech. The agreement gives us access to Genentech’s LRRK2 inhibitor program. As consideration to date, we have paid Genentech $12.5 million in the aggregate, including an upfront fee, a technology transfer fee and a clinical milestone payment, all of which was recorded as research and development expense as incurred. No amounts were recorded in the years ended December 31, 2019 or 2018. The first clinical milestone payment of $2.5 million was recorded as research and development expense during the year ended December 31, 2017.

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. These milestones include up to $37.5 million in clinical milestone payments, $102.5 million in regulatory milestone payments and $175.0 million in commercial milestone payments. In addition, we may owe 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.

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

Collaboration Revenue

To date, we have not generated any revenue from product sales and do not expect to generate any revenue from product sales for the foreseeable future. All revenue recognized to date has been collaboration revenue from our collaboration agreements with Takeda and Sanofi.

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

Operating Expenses

Research and Development

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

- external research and development expenses, including:
  - expenses incurred under arrangements with third parties, such as contract research organizations ("CROs"), preclinical testing organizations, contract development and manufacturing organizations ("CDMOs"), 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 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 late-stage IND-enabling studies.

Program expenses include expenses associated with our most advanced product candidates and the discovery and development of backup or next-generation molecules. We also track external expenses associated with our BBB platform technology. These expenses include those incurred by us relating to our Takeda Collaboration Agreement and Sanofi Collaboration Agreement. 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 rent and depreciation, and lab consumables.

It is challenging to predict the nature, timing and estimated long-range 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 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, depreciation and other expenses related to our office and research and development facility not otherwise included in research and development expenses.

We expect to continue to incur certain 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, insurance expenses, investor relations activities and other administrative and professional services. We also expect to increase our administrative headcount as we advance our product candidates through clinical development, which will also increase our general and administrative expenses.

Interest and Other Income, Net

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

Results of Operations

Comparison of the years ended December 31, 2019 and 2018

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

	Year Ended December 31,		Change	
	2019	2018	$	%
Collaboration revenue	$ 26,678	$ 129,160	$ (102,482)	(79) %
Operating expenses:				
Research and development	193,382	143,183	50,199	35
General and administrative	46,480	32,350	14,131	44
Total operating expenses	239,862	175,530	64,330	37
Loss from operations	(213,184)	(46,370)	(166,812)	360
Interest and other income, net	15,219	10,132	5,087	50
Loss before income taxes	(197,965)	(36,240)	(161,725)	446
Income tax benefit	351	—	351	100
Net loss	$ (197,614)	$ (36,240)	$ (161,374)	445 %

Collaboration revenue. Collaboration revenue was $26.7 million for the year ended December 31, 2019 compared to $129.2 million recognized for the year ended December 31, 2018. The decrease of $102.5 million was primarily due to a decrease of $102.7 million of revenue recognized under our Sanofi Collaboration Agreement in 2019.

Research and development expenses. Research and development expenses were $193.4 million for the year ended December 31, 2019 compared to $143.2 million for the year ended December 31, 2018.

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

	Year Ended December 31,		Change	
	2019	2018	$	%
LRRK2 program external expenses	$ 32,498	$ 13,167	$ 19,331	147 %
RIPK1 program external expenses	12,344	13,452	(1,108)	(8)
EIF2B program external expenses	5,411	2,498	2,913	117
ETV:IDS program external expenses	14,144	4,427	9,717	219
Other BBB program external expenses	14,303	5,448	8,855	163
BBB platform external expenses	1,784	29,827	(28,043)	(94)
Other external research and development expenses	17,667	8,859	8,808	99
Personnel related expenses[(1)]	62,527	41,923	20,604	49
Other unallocated research and development expenses	32,704	23,582	9,122	39
Total research and development expenses	$ 193,382	$ 143,183	$ 50,199	35 %

(1) Personnel-related expenses include stock-based compensation expense of $19.3 million and $10.1 million for the years ended December 31, 2019 and 2018, respectively, reflecting an increase of $9.2 million.

There was an increase in total research and development expenses of $50.2 million for the year ended December 31, 2019 compared to the year ended December 31, 2018. This reflects increases in external expenses related to progression of our portfolio, including the following: (i) an increase of $19.3 million in the LRRK2 program; (ii) an increase of $9.7 million in the ETV:IDS program; (iii) an increase of $8.9 million in other BBB delivery platform programs; (iv) an increase of $2.9 million in the EIF2B program; and (v) an increase of $8.8 million in other external research and development expenses. These increases were partially offset by a decrease of $1.1 million in RIPK1 program external expenses. Further, there was a $20.6 million increase in personnel-related expenses, consisting of a $11.4 million increase in salaries and related expenses attributable to an increase in our research and development headcount, and a $9.2 million increase in stock-based compensation expense primarily attributable to additional equity award grants and certain performance and market-based awards. There was also a $9.1 million increase in other unallocated research and development expenses, which was primarily due to an increase in facilities-related expenses of $5.4 million resulting from increased rent expense associated with the new headquarters lease, a $2.5 million increase in lab consumable expenses, and a $1.2 million increase in other general costs, such as travel and IT related expenses attributable to our research and development departments. These increases were partially offset by a $28.0 million decrease in BBB platform external expense, the majority of which related to expenses incurred in 2018 associated with the acquisition of F-star Gamma Limited, and the nomination of two additional Fcab targets under the F-star Collaboration Agreement, both of which occurred in May 2018.

General and administrative expenses. General and administrative expenses were $46.5 million for the year ended December 31, 2019 compared to $32.3 million for the year ended December 31, 2018. The increase of $14.1 million was primarily attributable to the $12.3 million increase in personnel-related expenses, driven by higher general and administrative headcount and stock-based compensation expense associated with additional equity award grants and certain performance and market-based awards. Additionally, there was a $1.0 million increase in facilities related expenses, including increased rent expense associated with the new headquarters lease and a $1.3 million increase in other general costs, such as travel, insurance, taxes and IT related expenses attributable to our general and administrative departments. These increases were partially offset by a $0.5 million decrease in legal and other professional service expenses.

Interest and other income, net. Interest and other income, net was $15.2 million for the year ended December 31, 2019 compared to $10.1 million for the year ended December 31, 2018. The increase of $5.1 million reflects higher interest income due to a higher average cash balance in the year ended December 31, 2019 compared to the year ended December 31, 2018. Further, we received $2.6 million of sublease income in the year ended December 31, 2019 but no sublease income for the year ended December 31, 2018.

Income tax benefit. Income tax benefit was $0.4 million for the year ended December 31, 2019 due to the tax benefit associated with an unrealized gain on marketable securities in other comprehensive income. There was no income tax benefit for the year ended December 31, 2018.

Comparison of the years ended December 31, 2018 and 2017

Refer to “Item 7. Management’s Discussion and Analysis of Financial Condition and Results of Operations—Results of Operations” in our 2018 Annual Report on Form 10-K for a discussion of the results of operations for the year ended December 31, 2018 compared to the year ended December 31, 2017.

Liquidity and Capital Resources

Sources of Liquidity

We have funded our operations primarily from the issuance and sale of convertible preferred stock, proceeds from our IPO, our follow on offering, and payments received from our collaboration agreements with Takeda and Sanofi. On December 7, 2017, we completed our IPO pursuant to which we issued 15,972,221 shares of our common stock, including 2,083,333 shares sold pursuant the underwriters' full exercise of their option to purchase additional shares, at a price of $18.00 per share. We received $264.3 million from our IPO, net of underwriting discounts and commissions, and offering expenses incurred by us.

Pursuant to the Takeda Collaboration Agreement, we have received $55.0 million related to upfront and milestone payments through December 31, 2019. Further, under the associated Purchase Agreement we received $110.0 million in February 2018 for the sale and issuance of 4,214,559 shares of our common stock.

Pursuant to the Sanofi Collaboration Agreement, we received an upfront payment of $125.0 million in November 2018, and a milestone payment of $10.0 million in August 2019, which was triggered by the commencement of a DNL758 Phase 1 clinical trial in healthy volunteers. We have received further payments of $11.6 million for performance of Retained Activities through December 31, 2019.

As of December 31, 2019, we had cash, cash equivalents and marketable securities in the amount of $455.2 million.

In January 2020, we sold 9.0 million shares of common stock (inclusive of shares sold pursuant to an overallotment option granted to the underwriters in connection with the offering) through an underwritten public offering at a price of $23.00 per share for aggregate net proceeds of approximately$194.1 million.

Future Funding Requirements

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

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

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

Since our inception, we have incurred significant losses and negative cash flows from operations. We have an accumulated deficit of $425.6 million through December 31, 2019. We expect to incur substantial additional losses in the future as we conduct and expand our research and development activities. We believe that our existing cash, cash equivalents and marketable securities will be sufficient to enable us to fund our projected operations through at least the next 12 months. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect. Our future funding requirements will depend on many factors, including:

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

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

Cash Flows

The following table summarizes our cash flow activity (in thousands):

	Year Ended December 31,		
	2019	2018	2017
Net cash provided by (used in) operating activities	$ (151,576)	$ 50,116	$ (76,635)
Net cash provided by (used in) investing activities	147,712	(287,422)	(41,166)
Net cash provided by financing activities	6,190	97,019	296,323
Net increase (decrease) in cash, cash equivalents and restricted cash	$ 2,326	$ (140,287)	$ 178,522

Net Cash Provided By (Used In) Operating Activities

During the year ended December 31, 2019, cash used in operating activities was $151.6 million, which consisted of a net loss of $197.6 million, adjusted by non-cash items primarily related to stock-based compensation, depreciation, and non-cash rent expenses, partially offset by net amortization of discounts on marketable securities. Cash used in operating activities was also driven by changes in our operating assets and liabilities.

Net Cash Provided By (Used In) Investing Activities

During the year ended December 31, 2019, cash provided by investing activities was $147.7 million, which consisted of $535.3 million in proceeds from the maturity of marketable securities, partially offset by $369.7 million of purchases of marketable securities and $17.9 million of capital expenditures to purchase property and equipment.

Net Cash Provided By Financing Activities

During the year ended December 31, 2019, cash provided by financing activities was $6.2 million, which consisted entirely of proceeds from the exercise of options to purchase common stock and issuance of shares pursuant to our employee stock purchase plan ("ESPP") shares.

Years ended December 31, 2018 and 2017

Refer to “Item 7. Management’s Discussion and Analysis of Financial Condition and Results of Operations—Liquidity and Capital Resources” in our 2018 Annual Report on Form 10-K for a discussion of the cash flows for the years ended December 31, 2018 and 2017.

Off-Balance Sheet Arrangements

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

Contractual Obligations and Commitments

The following table summarizes our contractual obligations as of December 31, 2019 (in thousands):

	Total	Less Than 1 Year	1-3 Years	3-5 Years	More Than 5 Years
Operating lease obligations (1)	$ 107,463	$ 9,737	$ 21,122	$ 22,530	$ 54,074
Obligations under license and other contractual agreements (2)	12,251	10,971	390	160	730
Total contractual obligations (3)	$ 119,714	$ 20,708	$ 21,512	$ 22,690	$ 54,804

(1) Represents future minimum lease payments under our headquarters lease. The minimum lease payments above do not include any related common area maintenance charges or real estate taxes.
(2) Represents non-cancellable fees due in connection with license and other contractual agreements, including those under the Lonza DMSA.
(3) We enter into contracts in the normal course of business, primarily with CROs for preclinical research studies and clinical trials, or for other services or supplies related to research and development activities. These contracts generally provide for termination on notice, and no arrangements include material stipulated commitment payments.

In May 2018, we entered into an amendment to our operating lease for our former corporate headquarters in South San Francisco (the "Headquarters Lease Amendment") to relocate and expand our headquarters to 148,020 rentable square feet in a building in South San Francisco, California (the "New Premises"). The Headquarters Lease Amendment has a contractual term of ten years from the legal commencement date, which was April 1, 2019 when the building was ready for occupancy. For accounting purposes, the lease commencement date was determined to be August 1, 2018, which was the date at which we were deemed to have obtained control over the property. We have an option to extend the lease term for a period of ten years by giving the landlord written notice of the election to exercise the option at least nine months, but not more than twelve months, prior to the expiration of the Headquarters Lease Amendment lease term. We determined that this renewal was not reasonably certain at lease inception.

The Headquarters Lease Amendment provides for monthly base rent amounts escalating over the term of the lease. In addition, the Headquarters Lease Amendment provided a tenant improvement allowance ("TIA") of up to $25.9 million, which was fully utilized, of which $4.4 million will be repaid to the landlord in the form of additional monthly rent. This is recorded as leasehold improvement assets and an offset to the lease ROU asset on the Consolidated Balance Sheet as of December 31, 2019. We are also required to pay the operating expenses for the New Premises, such as taxes and insurance, which are treated as variable lease payments.

Effective September 2017, we 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, 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 DMSA will expire on September 6, 2022.

As of December 31, 2019 and 2018, we had open non-cancellable purchase orders for biological product development and manufacturing costs totaling $21.2 million and $24.7 million, respectively. The activities under these purchase orders are expected to be completed by November 2024. As of December 31, 2019 and 2018, we had total non-refundable purchase commitments of $11.2 million and $14.0 million, respectively, under the DMSA.

During the years ended December 31, 2019 and 2018, we incurred costs of $12.7 million and $3.9 million, and made payments of $12.5 million and $3.4 million, respectively, for the development and manufacturing services rendered under the DMSA. We had not incurred any costs or made any payments for the development and manufacturing services rendered under the DMSA for the year ended December 31, 2017.

Pursuant to certain license agreements, including our agreement with Genentech, we have obligations to make future milestone and royalty payments to other parties. Additionally, we have certain contingent payments to F-star and former shareholders of F-star Gamma related to the acquisition of F-star Gamma, 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 and, therefore, any related payments are not included in the table above.

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 U.S. 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 revenues recognized and expenses incurred during the reporting periods. Our estimates are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. While our significant accounting policies are described in more detail in the notes to our consolidated financial statements included elsewhere in this report, 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.

Revenue Recognition

License and Collaboration Revenue

Effective January 1, 2018, we adopted Accounting Standards Codification (“ASC”), Topic 606, *Revenue from Contracts with Customers* (“Topic 606”), using a full retrospective application. There was no impact to the consolidated financial statements upon adoption of Accounting Standards Update ("ASU") 2014-09 as we had not recognized any revenue through December 31, 2017. This standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as collaboration arrangements and leases.

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

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

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

We record amounts received prior to satisfying the revenue recognition criteria as contract liabilities in our consolidated balance sheets. If the related performance obligation is expected to be satisfied within the next twelve months this will be classified in current liabilities. Amounts recognized as revenue prior to the Company having an unconditional right (other than a right that is conditioned only on the passage of time) to receipt are recorded as contract assets in our consolidated balance sheets. If we expect to have an unconditional right to receive the consideration in the next twelve months, this will be classified in current assets. A net contract asset or liability is presented for each contract with a customer.

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

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

If it is determined that multiple performance obligations exist, the transaction price is allocated at the inception of the agreement to all identified performance obligations based on the relative standalone selling prices ("SSP"). The relative SSP for each deliverable is estimated using external sourced evidence if it is available. If external sourced evidence is not available, we use our best estimate of the SSP for the deliverable.

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

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

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

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, CDMOs, 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.

Stock-Based Compensation

We have granted stock-based awards, consisting of stock options, restricted stock units, restricted stock awards, and shares issued under its employee stock purchase plan 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. Subsequent to the adoption of ASU No. 2018-07, *Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* on September 30, 2018, future stock-based compensation expense for non-employee stock-based awards is measured based on the fair value on the date of adoption. We recognize the corresponding compensation expense of awards over the requisite service period, which is generally the vesting period of the respective award, and we adjust for actual forfeitures as they occur.

We estimate the fair value of stock options granted to our employees and directors and rights to acquire stock granted under our ESPP, and the resulting stock-based compensation expense, using the Black-Scholes option-pricing model. We use the fair value of our common stock to determine the fair value of restricted stock awards.

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 we have very limited 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.

Determination of the estimated fair value of our common stock on grant dates prior to our IPO

As there was no public market for our common stock prior to our IPO, the estimated fair value of our common stock was 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.

We 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* ("Practice Aid"). In accordance with the Practice Aid, our board of directors considered the Current Value Method, the Option-Pricing Method, and the Probability-Weighted Expected Return Method in estimating the fair value of our common stock.

Our board of directors and management developed 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.

Determination of the fair value of our common stock on grant dates following our IPO

The fair value of each share of underlying common stock is based on the closing price of our common stock as reported by The NASDAQ Global Select Market on the date of grant.

In the past, we granted stock options that vest in conjunction with certain performance and market conditions to certain key employees. 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. In the event that neither of these market triggers are achieved by the specified timelines, such awards will terminate with respect to that portion of the shares. Expense is recognized using the accelerated attribution method and is recognized over the derived service period. We used a lattice model with a Monte Carlo simulation to value these performance and market contingent stock-based option awards. This valuation methodology utilized the estimated fair value of our common stock on grant date and several key assumptions, including expected volatility of our stock price based on comparable public companies, risk-free rates of return and expected dividend yield.

Stock-based compensation expense was $38.4 million, $18.8 million and $4.4 million for the years ended December 31, 2019, 2018, and 2017, respectively. As of December 31, 2019, we had $76.2 million of total unrecognized stock-based compensation expenses which we expect to recognize over a weighted-average period of 2.7 years.

We have not recognized, and we do not expect to recognize in the near future, any tax benefit related to employee stock-based compensation expense as a result of the full valuation allowance on our deferred tax assets including deferred tax assets related to our net operating loss carryforwards.

Leases

Effective January 1, 2019, we adopted Accounting Standards Codification (“ASC”), Topic 842, *Leases* (“Topic 842”), applying the optional transition method such that we are not required to adjust prior period presentations. ASU 2016-02 has impacted our Consolidated Balance Sheets as we have certain operating lease arrangements for which we are the lessee and one operating lease arrangement for which we are the lessor. We have no financing leases. We elected the package of practical expedients permitted under the transition guidance within the new standard, which among other things, allows us to carryforward the historical lease classification. The impact of adoption of the standard is that as of January 1, 2019 we recognized a ROU asset of $46.1 million and operating lease liability of $71.3 million. The standard did not have a material impact on our Consolidated Statements of Operations and Comprehensive Loss, Consolidated Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit), or Consolidated Statements of Cash Flows.

We make a determination as to whether an arrangement is a lease at inception. We recognize a right-of-use (“ROU”) asset and operating lease liability for identified operating leases in the Consolidated Balance Sheets.

ROU assets represent our right to use the underlying assets for the lease term and lease liabilities represent our obligation to make lease payments arising from the lease. We recognize operating lease ROU assets and liabilities at commencement date based on the present value of lease payments due over the lease term, with the ROU assets adjusted for lease incentives received. When determining the present value of lease payments, we use our incremental borrowing rate (“IBR”) on the date of lease commencement, or the rate implicit in the lease, if known. We do not assume renewals or early terminations in our determination of the lease term unless it is reasonably certain at lease inception to exercise these options.

We do not include leases with an initial term of 12 months or less on the balance sheet, unless they include an option to purchase the underlying asset which is reasonably certain of exercise. We recognize lease expenses on a straight-line basis over the lease term. We have leases with lease and non-lease components, which we have elected to account for as a single lease component.

Recent Accounting Pronouncements

See Note 1 to our consolidated financial statements included in Part II, Item 8, “Financial Statements and Supplementary Data,” of this Annual Report on Form 10-K for a description of recent accounting pronouncements applicable to our business.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

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

Interest Rate Sensitivity

We are exposed to market risk related to changes in interest rates. We had cash, cash equivalents and marketable securities of $455.2 million as of December 31, 2019, 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 policy. 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 British Pound, and we therefore are subject to foreign exchange risk. The fluctuation in the value of the U.S. dollar against other currencies affects the reported amounts of expenses, assets and liabilities primarily associated with a limited number of preclinical, clinical and manufacturing activities.

We seek to mitigate the impact of changes in currency exchange rates on cash flows from certain foreign currency denominated operating expenses by entering into forward foreign currency exchange contracts. Generally, the market risks of these contracts are offset by the corresponding gains and losses on the transactions being hedged.

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

As of December 31, 2019, we had open forward foreign currency exchange contracts with notional amounts of $4.8 million. A hypothetical 10% strengthening in foreign currency compared with the U.S. dollar at December 31, 2019 would have resulted in an increase in the value received over the remaining life of these contracts of approximately $0.5 million and, if realized, would positively affect earnings during the remaining life of the contracts. This analysis does not consider the impact of the hypothetical changes in foreign currency rates would have on the forecasted transactions that these foreign currency sensitive instruments were designated to offset.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA

Denali Therapeutics Inc.
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Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Denali Therapeutics Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Denali Therapeutics Inc. (the Company) as of December 31, 2019 and 2018, the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders' equity (deficit) and cash flows for each of the three years in the period ended December 31, 2019, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2019 and 2018, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2019, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the Company's internal control over financial reporting as of December 31, 2019, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) and our report dated February 27, 2020 expressed an unqualified opinion thereon.

Adoption of ASU No. No. 2016-02

As discussed in Note 1 to the consolidated financial statements, the Company changed its method of accounting for leases in 2019 due to the adoption of Accounting Standards Update (ASU) No. 2016-02, Leases (Topic 842), and the related amendments.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

The critical audit matter communicated below is a matter arising from the current period audit of the financial statements that was communicated or required to be communicated to the audit committee and that: (1) relates to accounts or disclosures that are material to the financial statements and (2) involved our especially challenging, subjective, or complex judgments. The communication of the critical audit matter does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Accounting for Revenue from Collaboration Agreements

Description of the Matter	Collaboration revenue recognized from the Company's collaboration and license agreements was $26.7 million for the year ended December 31, 2019. As discussed in Note 6 to the consolidated financial statements, the Company entered into a Collaboration and License Agreement and a Collaboration and Option Agreement with Genzyme Corporation and Takeda Pharmaceutical Company Limited, respectively, during 2018 to develop and commercialize various research programs. The Company is recognizing the revenue allocated to certain performance obligations using an input method, which involves the measurement of progress toward each performance obligation based on a measurement of the actual costs incurred for the related research and development activities for each program compared to the total costs expected to be incurred to satisfy the respective obligation. Auditing the Company's estimated measure of progress was complex. The Company's estimate of costs expected to be incurred in the future requires estimation of the amounts it expects to incur for research and development by project.
How We Addressed the Matter in Our Audit	We obtained an understanding, evaluated the design and tested the operating effectiveness of controls over the Company's collaboration revenue process, including controls over the identification of actual costs incurred and the Company's estimation of total expected costs used in its measure of progress calculations, as well as controls over the completeness and accuracy of data used in the calculations. Our audit procedures included, among others, gaining an understanding and testing the significant assumptions used in the Company's estimates of total expected costs by project, and testing the completeness and accuracy of the underlying data used by the Company in its revenue recognition model. We performed inquiries of the research and development personnel responsible for the specific development projects to corroborate management's assumptions used in the Company's estimates of total expected costs by project, reviewed any changes in the product development timeline and/or increases or decreases in the total expected costs by project on a quarterly basis, and examined evidence supporting key inputs of the revenue recognition model including assessing whether actual costs incurred were appropriate under the terms of the respective contracts. We compared the estimates of total expected costs by project to actual costs incurred on a quarterly basis to evaluate management's ability to forecast costs. We also tested the amount of historical costs incurred under each project and the calculation of amounts recognized under the revenue recognition model.

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2015.

Redwood City, California
February 27, 2020

Denali Therapeutics Inc.

Consolidated Balance Sheets
(In thousands, except share amounts)

	December 31, 2019	December 31, 2018
Assets		
Current assets:		
Cash and cash equivalents	$ 79,449	$ 77,123
Short-term marketable securities	335,907	387,174
Prepaid expenses and other current assets	14,675	16,539
Total current assets	430,031	480,836
Long-term marketable securities	39,886	147,881
Property and equipment, net	46,732	25,162
Operating lease right-of-use asset	33,923	—
Other non-current assets	2,659	8,105
Total assets	$ 553,231	$ 661,984
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 2,590	$ 1,891
Accrued expenses and other current liabilities	24,015	19,468
Contract liabilities	18,739	11,427
Total current liabilities	45,344	32,786
Contract liabilities, less current portion	43,753	57,350
Operating lease liability, less current portion	68,865	—
Deferred rent, less current portion	—	24,532
Other non-current liabilities	379	471
Total liabilities	158,341	115,139
Commitments and contingencies (Note 9)		
Stockholders' equity:		
Convertible preferred stock, $0.01 par value; 40,000,000 shares authorized as of December 31, 2019 and December 31, 2018; 0 shares issued and outstanding as of December 31, 2019 and December 31, 2018	—	—
Common stock, $0.01 par value; 400,000,000 shares authorized as of December 31, 2019 and December 31, 2018; 96,189,935 and 94,662,435 shares issued and outstanding as of December 31, 2019 and December 31, 2018, respectively	1,288	1,273
Additional paid-in capital	818,803	774,158
Accumulated other comprehensive income (loss)	350	(649)
Accumulated deficit	(425,551)	(227,937)
Total stockholders' equity	394,890	546,845
Total liabilities and stockholders' equity	$ 553,231	$ 661,984

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,		
	2019	2018	2017
Collaboration revenue	$ 26,678	$ 129,160	$ —
Operating expenses:			
Research and development	193,382	143,183	74,460
General and administrative	46,480	32,349	15,680
Total operating expenses	239,862	175,532	90,140
Loss from operations	(213,184)	(46,372)	(90,140)
Interest and other income, net	15,219	10,132	1,955
Loss before income taxes	(197,965)	(36,240)	(88,185)
Income tax benefit	351	—	—
Net loss	(197,614)	(36,240)	(88,185)
Other comprehensive income (loss):			
Net unrealized gain (loss) on marketable securities, net of tax	999	(281)	5
Comprehensive loss	$ (196,615)	$ (36,521)	$ (88,180)
Net loss per share, basic and diluted	$ (2.07)	$ (0.39)	$ (5.89)
Weighted average number of shares outstanding, basic and diluted	95,608,208	92,621,991	14,964,144

See accompanying notes to consolidated financial statements.

Denali Therapeutics Inc.

Consolidated Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit)
(In thousands, except share amounts)

	Convertible Preferred Stock		Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount				
Balance at December 31, 2016	58,600,315	$ 348,673	8,597,316	$ 344	$ 9,387	$ (373)	$ (103,512)	$ (94,154)
Issuance of series B-2 convertible preferred stock for cash, net of issuance costs of $73	1,764,705	29,927	—	—	—	—	—	—
Conversion of Series A and B convertible preferred stock into common stock	(60,365,020)	(378,600)	60,365,020	604	377,996	—	—	378,600
Issuance of common stock upon initial public offering, net of issuance costs of $23,612	—	—	15,972,221	160	264,101	—	—	264,261
Issuance of common stock upon exercise of stock options	—	—	648,317	25	708	—	—	733
Issuance of reserved common stock as consideration in asset acquisition	—	—	81,164	1	(1)	—	—	—
Vesting of early exercised common stock	—	—	187,500	6	121	—	—	127
Vesting of restricted stock awards	—	—	1,628,824	61	(61)	—	—	—
Stock-based compensation	—	—	—	—	4,409	—	—	4,409
Net loss	—	—	—	—	—	—	(88,185)	(88,185)
Other comprehensive income	—	—	—	—	—	5	—	5
Balance at December 31, 2017	—	—	87,480,362	1,201	656,660	(368)	(191,697)	465,796
Issuance of common stock in connection with the Takeda Collaboration Agreement	—	—	4,214,559	42	94,364	—	—	94,406
Issuances under equity incentive plans	—	—	792,939	8	3,991	—	—	3,999
Vesting of early exercised common stock	—	—	234,372	3	371	—	—	374
Vesting of restricted stock awards	—	—	1,940,203	19	(19)	—	—	—
Stock-based compensation	—	—	—	—	18,791	—	—	18,791
Net loss	—	—	—	—	—	—	(36,240)	(36,240)
Other comprehensive loss	—	—	—	—	—	(281)	—	(281)
Balance at December 31, 2018	—	—	94,662,435	1,273	774,158	(649)	(227,937)	546,845
Issuances under equity incentive plans	—	—	973,012	9	6,181	—	—	6,190
Vesting of early exercised common stock	—	—	135,424	2	90	—	—	92
Vesting of restricted stock awards and units	—	—	419,064	4	(4)	—	—	—
Stock-based compensation	—	—	—	—	38,378	—	—	38,378
Net loss	—	—	—	—	—	—	(197,614)	(197,614)
Other comprehensive income	—	—	—	—	—	999	—	999
Balance at December 31, 2019	—	$ —	96,189,935	$ 1,288	$ 818,803	$ 350	$ (425,551)	$ 394,890

See accompanying notes to consolidated financial statements.

Denali Therapeutics Inc.

Consolidated Statements of Cash Flows
(In thousands)

	Year Ended December 31,		
	2019	**2018**	**2017**
Operating activities			
Net loss	$ (197,614)	$ (36,240)	$ (88,185)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:			
Depreciation and amortization	7,991	7,415	3,082
Stock-based compensation expense	38,378	18,791	4,409
Net amortization of (discounts) and premiums on marketable securities	(5,019)	(2,705)	753
Non-cash operating lease expense	864	—	—
Other non-cash items	(351)	(36)	1
Changes in operating assets and liabilities:			
Prepaid expenses and other assets	6,675	(18,290)	73
Accounts payable	1,033	(526)	207
Accrued and other current liabilities	1,500	9,113	3,578
Contract liability	(6,286)	68,777	—
Deferred rent	—	3,438	—
Operating lease liability	1,253	—	—
Other non-current liabilities	—	379	(553)
Net cash provided by (used in) operating activities	(151,576)	50,116	(76,635)
Investing activities			
Purchase of marketable securities	(369,696)	(557,930)	(179,789)
Purchase of property and equipment	(17,919)	(3,393)	(2,875)
Maturities and sales of marketable securities	535,327	273,901	141,498
Net cash provided by (used in) investing activities	147,712	(287,422)	(41,166)
Financing activities			
Payments of issuance costs related to issuance for common stock	—	(1,342)	—
Payments of issuance costs related to issuance for preferred stock	—	(44)	—
Issuance of common stock in connection with the Takeda Collaboration Agreement	—	94,406	—
Proceeds from exercise of awards under equity incentive plans	6,190	3,999	733
Proceeds from issuance of common stock, net of issuance costs	—	—	265,619
Proceeds from issuance of convertible preferred stock, net of issuance costs	—	—	29,971
Net cash provided by financing activities	6,190	97,019	296,323
Net increase (decrease) in cash, cash equivalents and restricted cash	2,326	(140,287)	178,522
Cash, cash equivalents and restricted cash at beginning of year	78,623	218,910	40,388
Cash, cash equivalents and restricted cash at end of year	$ 80,949	$ 78,623	$ 218,910
Supplemental disclosures of cash flow information			
Tenant improvements provided by the landlord	$ 11,343	$ 14,561	$ —
Property and equipment purchases accrued but not yet paid	$ —	$ 335	$ 103
Deferred IPO costs incurred but not yet paid	$ —	$ —	$ 1,358
Convertible preferred stock issuance costs incurred but not yet paid	$ —	$ —	$ 44

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 neurodegenerative diseases. 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") and pursuant to the rules and regulations of the Securities and Exchange Commission ("SEC").

Reverse Stock Split

In November 2017, the Company's board of directors and stockholders approved an amendment to the Company's amended and restated certificate of incorporation to effect a reverse split of shares of its common stock and convertible preferred stock on a 4-to-1 basis (the "Reverse Stock Split"). The par values and the authorized shares of the common and convertible preferred stock were not adjusted as a result of the Reverse Stock Split. The Reverse Stock Split became effective on November 28, 2017. All issued and outstanding common stock and convertible preferred stock and related per share amounts contained in the financial statements have been retroactively adjusted to reflect this Reverse Stock Split for all periods presented.

Initial Public Offering

On December 7, 2017, the Company's Registration Statement on Form S-1 was declared effective by the SEC for our initial public offering ("IPO") of common stock. The Company's shares started trading on the NASDAQ Global Select Market on December 8, 2017, and the transaction formally closed on December 12, 2017. In connection with the IPO, the Company sold an aggregate of 15,972,221 shares of common stock, including 2,083,333 shares sold pursuant to the underwriters' full exercise of their option to purchase additional shares, at a price to the public of $18.00 per share. The aggregate net proceeds received by the Company from the offering, net of underwriting discounts and commissions and offering expenses, were $264.3 million. Upon the closing of the IPO, all then-outstanding shares of the Company's convertible preferred stock converted into 60,365,020 shares of common stock. The related carrying value of $378.6 million was reclassified to common stock and additional paid-in capital. Additionally, the Company amended and restated its certificate of incorporation effective December 7, 2017 to, among other things, change the authorized number of shares of common stock to 400,000,000 shares and the authorized number of shares of preferred stock to 40,000,000 shares.

Principles of Consolidation

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

Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires the Company to make certain estimates, judgments and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the 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 Balance Sheets and Statements of Operations and Comprehensive Loss.

Concentration of Credit Risk and Other Risks and Uncertainties

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

The Company’s investment policy limits investments to certain types of securities issued by the U.S. government, its agencies and institutions with investment-grade credit ratings and places restrictions on maturities and concentration by type and issuer. The Company is exposed to credit risk in the event of a default by the financial institutions holding its cash, cash equivalents and marketable securities and issuers of marketable securities to the extent recorded on the Consolidated Balance Sheets. As of December 31, 2019 and 2018, the Company had no off-balance sheet concentrations of credit risk.

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

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

Segments

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

Fair Value of Financial Instruments

Accounting Standards Codification ("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, Cash Equivalents and Restricted Cash

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 are stated at fair value.

The Company’s restricted cash consists of the letter of credit for the Company’s headquarters building lease, and is included within other non-current assets on the accompanying Consolidated Balance Sheets.

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’ equity (deficit). We classify investments in securities with remaining maturities of less than one year, or where our intent is to use the investments to fund current operations or to make them available for current operations, as short-term investments. We classify investments in securities with remaining maturities of over one year as long-term investments. The amortized cost of debt securities is adjusted for amortization of premiums and accretion of discounts to maturity, which is included in interest and other income, net in the Consolidated Statements of Operations and Comprehensive Loss. Realized gains and losses and declines in value judged to be other-than-temporary, if any, on marketable securities are included in interest and other 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.

Accounts Receivable

Accounts receivable are included within prepaid expenses and other current assets in the Consolidated Balance Sheets. The accounts receivable balance represents amounts receivable from the Company's collaboration partners. The Company estimates the allowance for doubtful accounts based on existing contractual payment terms, actual payment patterns of its partners, and individual partner circumstances. To date, an allowance for doubtful accounts has not been required.

Derivatives and Hedging Activities

The Company accounts for its derivative instruments as either assets or liabilities on the Consolidated Balance Sheets and measures them at fair value. Derivatives are adjusted to fair value through interest and other income, net in the Consolidated Statements of Operations and Comprehensive Loss.

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.

Asset	**Estimated useful life**
Leasehold improvements	Shorter of life of asset or lease term
Manufacturing and laboratory equipment	five years
Computer hardware and software	three years
Office furniture and equipment	five 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.

Leases

The Company adopted Accounting Standards Update ("ASU") No. 2016-02, *Leases,* as of January 1, 2019. A determination is made as to whether an arrangement is a lease at inception. A right-of-use ("ROU") asset and operating lease liability is recognized for identified operating leases in the Consolidated Balance Sheets.

ROU assets represent the Company's right to use the underlying asset for the lease term and lease liabilities represent the Company's obligation to make lease payments arising from the lease. Operating lease ROU assets and liabilities are recognized at the lease commencement date based on the present value of lease payments due over the lease term, with the ROU assets adjusted for lease incentives received. When determining the present value of lease payments, the Company uses its incremental borrowing rate ("IBR") on the date of lease commencement, or the rate implicit in the lease, if known. The Company does not assume renewals in its determination of the lease term unless the renewals are deemed by management to be reasonably certain at lease inception.

Leases with an initial term of 12 months or less are not recorded on the balance sheet, unless they include an option to purchase the underlying asset that the Company is reasonably certain to exercise. The Company recognizes lease expenses on a straight-line basis over the lease term. The Company has leases with lease and non-lease components, which the Company has elected to account for as a single lease component. The current operating lease liability is included within accrued expenses and other current liabilities on the Consolidated Balance Sheet.

Revenue Recognition

License and Collaboration Revenue

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

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

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

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

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

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

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

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

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

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

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 received 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's stock-based compensation programs grant awards that have included stock options, restricted stock units, restricted stock awards, and shares issued under its employee stock purchase plan. Grants are awarded to employees, including directors, and non-employees.

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. Subsequent to the adoption of ASU No. 2018-07, *Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* on September 30, 2018, future stock-based compensation expense for non-employee stock-based awards is measured based on the fair value on the date of adoption. 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 uses the fair value of our common stock to determine the fair value of restricted stock awards.

Income Taxes

Income taxes are accounted for using the liability method, under which deferred tax assets and liabilities are determined based on the temporary 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. Previously recognized tax positions that no longer meet the more-likely-than-not threshold are derecognized in the first subsequent financial reporting period in which that threshold is no longer met.

The Company's policy is to recognize interest and penalties accrued on any unrecognized tax benefits as a component of income tax expense.

Comprehensive Income (Loss)

Comprehensive income (loss) is composed of net loss and certain changes in stockholders' equity (deficit) that are excluded from net loss, primarily unrealized gains or losses on the Company's marketable securities.

Net Income (Loss) per Share

Basic net income (loss) per share is calculated by dividing the net income (loss) by the weighted-average number of shares of common stock outstanding during the period, without consideration for common stock equivalents.

Diluted net income per ordinary share is computed by giving effect to all dilutive potential ordinary shares including options. However, where there is a diluted net loss per ordinary share, no adjustment is made for potentially issuable ordinary shares since their effect would be anti-dilutive. In this case, diluted net loss per share is equal to basic net loss per share.

Recently Issued Accounting Pronouncements

In June 2016, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update No. 2016-13, *Financial Instruments-Credit Losses: Measurement of Credit Losses on Financial Instruments*. ASU 2016-13 requires measurement and recognition of expected credit losses for financial assets. In April 2019, the FASB issued clarification to ASU 2016-13 within ASU 2019-04, *Codification Improvements to Topic 326, Financial Instruments-Credit Losses, Topic 815, Derivatives and Hedging*, *and Topic 825, Financial Instruments*. The guidance will become effective as of January 1, 2020, and must be adopted using a modified retrospective approach, with certain exceptions. The Company plans to adopt this standard on January 1, 2020, and is substantially complete with its evaluation of the effect that the adoption of this ASU will have on its Consolidated Financial Statements. The Company does not expect any impact to the Consolidated Financial Statements. The only impact is expected to be in the applicable disclosures included in the Significant Accounting Policies and Cash and Marketable Securities footnotes.

In December 2019, the FASB issued Accounting Standards Update No. 2019-12, *Income Taxes (Topic 740) Simplifying the Accounting for Income Taxes.* ASU No. 2019-12 modifies ASC 740 to simplify several aspects of accounting for income taxes, including eliminating certain exceptions to the guidance in ASC 740 related to the approach for intraperiod tax allocation. The guidance is effective for fiscal years beginning after December 15, 2020 and interim periods within those fiscal years, with early adoption permitted, and is required to be adopted prospectively, with the exception of certain specific amendments. The Company is currently assessing the impact of this ASU on its Consolidated Financial Statements.

Recently Adopted Accounting Pronouncements

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842)*, which supersedes the guidance in former ASC 840, *Leases*. The FASB issued further updates to this guidance in July 2018 through ASU 2018-10, C*odification Improvements to Topic 842, Leases* and ASU 2018-11, *Leases (Topic 842): Targeted Improvements*, in December 2018 through ASU 2018-20, *Leases (Topic 842): Narrow-Scope Improvements for Lessors* and in March 2019 through ASU 2019-01 *Leases (Topic 842): Codification Improvements*. The new standard requires lessees to apply a dual approach, classifying leases as either finance or operating leases based on the principle of whether or not the lease is effectively a financed purchase by the lessee. This classification will determine whether lease expense is recognized based on an effective interest method or on a straight-line basis over the term of the lease. A lessee is also required to record a right-of-use asset and a lease liability for all leases with a term of greater than 12 months regardless of their classification. The standard was effective for interim and annual periods beginning after December 15, 2018, with early adoption permitted, and was required to be adopted using a modified retrospective approach.

The Company adopted this standard as of January 1, 2019, applying the optional transition method such that it is not required to adjust prior period presentations. ASU 2016-02 has impacted the Company's Consolidated Balance Sheet as the Company has certain operating lease arrangements for which the Company is the lessee and one operating lease arrangement for which the Company is the lessor. The Company has no financing leases. Management has elected the package of practical expedients permitted under the transition guidance within the new standard, which among other things, allows the Company to carryforward the historical lease classification. The impact of adoption of the standard is that as of January 1, 2019, the Company recognized a ROU asset of $46.1 million and operating lease liability of $71.3 million. The standard did not have a material impact on the Company's Consolidated Statements of Operations and Comprehensive Loss, Convertible Preferred Stock and Stockholders's Equity (Deficit) or Consolidated Statements of Cash Flows.

2. Fair Value Measurements

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

	December 31, 2019			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash equivalents:				
Money market funds	$ 54,163	$ —	$ —	$ 54,163
U.S. government treasuries	15,989	—	—	15,989
Short-term marketable securities:				
U.S. government treasuries	250,070	—	—	250,070
U.S. government agency securities	—	2,000	—	2,000
Corporate debt securities	—	53,479	—	53,479
Commercial paper	—	30,358	—	30,358
Long-term marketable securities:				
U.S. government treasuries	13,869	—	—	13,869
Corporate debt securities	—	26,017	—	26,017
Foreign currency derivative contracts	—	85	—	85
Total	$ 334,091	$ 111,939	$ —	$ 446,030
Liabilities:				
Foreign currency derivative contracts	$ —	$ 8	$ —	$ 8
Total	$ —	$ 8	$ —	$ 8

	December 31, 2018			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash equivalents				
Money market funds	$ 42,225	$ —	$ —	$ 42,225
U.S. government treasuries	1,499	—	—	1,499
Commercial paper	—	9,979	—	9,979
Short-term marketable securities:				
U.S. government treasuries	219,754	—	—	219,754
U.S. government agency securities	—	73,151	—	73,151
Corporate debt securities	—	71,675	—	71,675
Commercial paper	—	22,594	—	22,594
Long-term marketable securities:				
U.S. government treasuries	117,131	—	—	117,131
U.S. government agency securities	—	1,977	—	1,977
Corporate debt securities	—	28,773	—	28,773
Foreign currency derivative contracts	—	14	—	14
Total	$ 380,609	$ 208,163	$ —	$ 588,772
Liabilities:				
Foreign currency derivative contracts	$ —	$ 182	$ —	$ 182
Total	$ —	$ 182	$ —	$ 182

The carrying amounts of prepaid expenses and other current assets, 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 years ended December 31, 2019 or 2018.

3. Cash and Marketable Securities

Cash, cash equivalents and restricted cash

A reconciliation of cash, cash equivalents, and restricted cash reported within the Consolidated Balance Sheets to the amount reported within the Consolidated Statements of Cash Flows is shown in the table below (in thousands):

	December 31, 2019	December 31, 2018	December 31, 2017
Cash and cash equivalents	$ 79,449	$ 77,123	$ 218,375
Restricted cash included within prepaid expenses and other current assets	—	—	84
Restricted cash included within other non-current assets	1,500	1,500	451
Total cash, cash equivalents, and restricted cash	$ 80,949	$ 78,623	$ 218,910

Marketable securities

All marketable securities were considered available-for-sale at December 31, 2019 and 2018. On a recurring basis, the Company records its marketable securities at fair value using Level 1 or Level 2 inputs as discussed in Note 2, "Fair Value Measurements". The amortized cost, gross unrealized holding gains or losses, and fair value of the Company's marketable securities by major security type at each balance sheet date are summarized in the tables below (in thousands):

	December 31, 2019			
	Amortized Cost	Unrealized Holding Gains	Unrealized Holding Losses	Aggregate Fair Value
Short-term marketable securities:				
U.S. government treasuries	$ 249,478	$ 594	$ (2)	$ 250,070
U.S. government agency securities	1,999	1	—	2,000
Corporate debt securities	53,396	94	(11)	53,479
Commercial paper	30,358	—	—	30,358
Total short-term marketable securities	335,231	689	(13)	335,907
Long-term marketable securities:				
U.S. government treasuries	13,865	6	(2)	13,869
Corporate debt securities	25,998	34	(15)	26,017
Total long-term marketable securities	39,863	40	(17)	39,886
Total	$ 375,094	$ 729	$ (30)	$ 375,793

	December 31, 2018			
	Amortized Cost	Unrealized Holding Gains	Unrealized Holding Losses	Aggregate Fair Value
Short-term marketable securities:				
U.S. government treasuries	$ 220,081	$ 29	$ (356)	$ 219,754
U.S. government agency securities	73,373	—	(222)	73,151
Corporate debt securities	71,940	1	(266)	71,675
Commercial paper	22,594	—	—	22,594
Total short-term marketable securities	387,988	30	(844)	387,174
Long-term marketable securities:				
U.S. government treasuries	116,878	329	(76)	117,131
U.S. government agency securities	1,975	2	—	1,977
Corporate debt securities	28,864	8	(99)	28,773
Total long-term marketable securities	147,717	339	(175)	147,881
Total	$ 535,705	$ 369	$ (1,019)	$ 535,055

As of December 31, 2019 and 2018, some of the Company’s marketable securities were in an unrealized loss position. The Company determined that it had the ability and intent to hold all marketable securities that have been in a continuous loss position until maturity or recovery, thus there was no recognition of any other-than-temporary impairment as of December 31, 2019 or 2018. All marketable securities with unrealized losses as of each balance sheet date have been in a loss position for less than twelve months or the loss is not material.

The Company recorded unrealized gains on marketable securities as other comprehensive income in the year ended December 31, 2019. As a result, the Company recorded a tax benefit of $0.4 million for the year ended December 31, 2019 on the Consolidated Statements of Operations and Comprehensive Loss and a corresponding tax charge in other comprehensive income. There were no unrealized gains in other comprehensive income during in the years ended 2018, or 2017, and as such there was no tax benefit recorded for the years ended December 31, 2018 and 2017 on the Consolidated Statements of Operations and Comprehensive Loss.

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

4. Derivative Financial Instruments

Foreign Currency Exchange Rate Exposure

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

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

The following table summarizes the Company’s forward foreign currency exchange contracts outstanding as of December 31, 2019 (notional amounts in thousands):

Foreign Exchange Contracts	Number of Contracts	Aggregate Notional[1] Amount in Foreign Currency	Maturity
Euros	23	1,500	Jan 2020 - Nov 2020
British Pounds	15	2,285	Jan 2020 - Jun 2020
Swiss Francs	10	129	Jan 2020 - Aug 2020
Total	48		

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

An immaterial derivative liability balance is recorded in other current liabilities on the Consolidated Balance Sheet as of December 31, 2019, and a derivative liability balance of $0.2 million is recorded in other current liabilities on the Consolidated Balance Sheet as of December 31, 2018. Immaterial derivative asset balances are recorded in prepaid assets and other current assets on the Consolidated Balance Sheets as of December 31, 2019 and 2018. A net gain of $0.2 million, and a net loss of $0.2 million, each associated with the Company's derivative instruments, are recognized in interest and other income, net on the Consolidated Statement of Operations and Comprehensive Loss for the years ended December 31, 2019 and 2018, respectively.

5. Acquisition

In August 2016, the Company entered into a License and Collaboration Agreement (“F-star Collaboration Agreement”) with F-star Gamma Limited (“F-star Gamma”), F-star Biotechnologische Forschungs-Und Entwicklungsges M.B.H ("F-star GmbH") and F-star Biotechnology Limited ("F-star Ltd") (collectively, “F-star”) to leverage F-star’s modular antibody technology and the Company’s expertise in the development of therapies for neurodegenerative diseases. Under the F-star Collaboration Agreement, the Company made payments to F-star totaling $11.5 million. In connection with the entry into the F-star Collaboration Agreement, the Company also purchased an option for an upfront option fee of $0.5 million (the “buy-out-option”), to acquire all of the outstanding shares of F-star Gamma pursuant to a pre-negotiated buy-out option agreement (the “Option Agreement”).

In May 2018, the Company exercised the Option Agreement and entered into a Share Purchase Agreement (the “Purchase Agreement”) with the shareholders of F-star Gamma and Shareholder Representative Services LLC, pursuant to which the Company acquired all of the outstanding shares of F-star Gamma (the “Acquisition”).

As a result of the Acquisition, F-star Gamma became a wholly-owned subsidiary of the Company and the Company changed the entity’s name to Denali BBB Holding Limited. In addition, the Company became a direct licensee of certain intellectual property of F-star Ltd by way of the Company’s assumption of F-star Gamma’s license agreement with F-star Ltd, dated August 24, 2016, (the “F-star Gamma License”). The Company made initial exercise payments under the Purchase Agreement and the F-star Gamma License, in the aggregate, of $17.8 million. In addition, the Company is required to make future contingent payments, to F-star Ltd and the former shareholders of F-star Gamma, up to a maximum amount of $447.0 million in the aggregate upon the achievement of certain defined preclinical, clinical, regulatory and commercial milestones. These include up to $27.0 million in preclinical contingent payments, $50.0 million in clinical contingent payments, $120.0 million in regulatory contingent payments and $250.0 million in commercial contingent payments. The amount of the contingent payments will vary based on whether F-star delivers an Fcab (constant Fc-domains with antigen-binding activity) that meets pre-defined criteria and whether the Fcab has been identified solely by the Company or solely by F-star or jointly by the Company and F-star. In June 2019, the Company made a payment of $1.5 million to F-star Ltd upon the achievement of a specified preclinical milestone in the Company's ETV:IDS program.

The Company concluded that the assets acquired and liabilities assumed upon the exercise of the Option Agreement did not meet the accounting definition of a business, and as such, the acquisition was accounted for as an asset purchase. The Company recognized $1.5 million and $18.3 million of contingent consideration as research and development expense in the years ended December 31, 2019 and 2018 respectively. As the transaction was accounted for as an asset purchase rather than a business combination, the Company did not recognize any contingent consideration on the acquisition date. Further future contingent consideration is expected to be recognized in research and development expense as incurred.

Under the F-star Collaboration Agreement, the Company is responsible for certain research costs incurred by F-star Ltd in conducting activities under an agreed development plan for each Fcab, for up to 24 months after the target Fcab is accepted. The Company's responsibility for research costs under the first development plan related to an Fcab that targets the transferrin receptor was completed during the year ended December 31, 2018. The responsibility for costs under the second development plan related to an undisclosed Fcab target commenced in February 2019. The Company recognized $1.1 million, $0.8 million, and $1.1 million in research and development expense related to the funding of F-star activities under these development plans during the years ended December 31, 2019, 2018, and 2017, respectively.

6. Collaboration Agreements

Sanofi

In October 2018, the Company entered into a Collaboration and License Agreement ("Sanofi Collaboration Agreement") with Genzyme Corporation, a wholly owned subsidiary of Sanofi S.A. ("Sanofi") pursuant to which certain small molecule CNS and peripheral RIPK1 inhibitors contributed by Sanofi and by Denali will be developed and commercialized. The Sanofi Collaboration Agreement became effective in November 2018 when the HSR requirements were satisfied at which time Sanofi paid the Company an upfront payment of $125.0 million. Under the Sanofi Collaboration Agreement, Denali is eligible to receive milestone payments from Sanofi up to approximately $1.1 billion upon achievement of certain clinical, regulatory and sales milestone events. Such milestone payments include $215.0 million in clinical milestone payments and $385.0 million in regulatory milestone payments for CNS Products, as defined, that are developed and approved in the United States, by the European Medicines Agency ("EMA") and in Japan for three indications, including Alzheimer's disease. These milestones also include $120.0 million in clinical milestone payments, $175.0 million in regulatory milestone payments and $200.0 million in commercial milestone payments for Peripheral Products, as defined, that are developed and approved in the United States, by the EMA and Japan for three indications.

Denali will share profits and losses equally with Sanofi for CNS Products sold in the United States and China, and receive variable royalties on net sales for CNS Products sold outside of the United States and China and for Peripheral Products sold worldwide.

Denali and Sanofi will jointly develop CNS Products pursuant to a global development plan. The Company will be responsible, at its own cost, for conducting Phase 1 and Phase 2 trials for CNS Products in Alzheimer’s disease and any activities required to support such clinical trials and specific for Alzheimer’s disease. Denali is conducting, at Sanofi’s cost, a Phase 1b trial for the lead CNS penetrant RIPK1 inhibitor, DNL747, in ALS. Sanofi is responsible, at its cost, for all other Phase 1 and Phase 2 trials for CNS Products, including for multiple sclerosis. Sanofi will lead the conduct of all Phase 3 and later stage development trials for CNS Products, with Sanofi and Denali funding 70% and 30% of such costs, respectively. Sanofi will also lead the commercialization activities globally for CNS Products, subject to certain options that Denali has to conduct co-commercialization activities with respect to each CNS Product in the United States and China.

Sanofi will be responsible, at its cost, for conducting activities relating to the development and commercialization of all Peripheral Products. Denali will be entitled to receive tiered royalties in the low- to mid- teen percentages on net sales of Peripheral Products.

The Company identified the following distinct performance obligations associated with the Sanofi Collaboration Agreement upon inception: the CNS program license, the Peripheral program license, the Phase 1 and Phase 2 trials for CNS Products for Alzheimer’s disease ("Alzheimer's Disease Services"), and the Phase 1b trial for DNL747 for ALS and associated activities ("Retained Activities").

The Company believes that the Sanofi Collaboration Agreement is a collaboration arrangement as defined in ASC 808, Collaborative Agreements. The Company also believes that Sanofi meets the definition of a customer as defined in ASC 606, Revenue From Contracts With Customers for three of the performance obligations identified at inception, but does not meet the definition of a customer for the Alzheimer's Disease Services. Further, Sanofi does not meet the definition of a customer for all Phase 3 and later stage development trials for CNS Products led by Sanofi for which Denali will fund 30% of total costs. Since ASC 808 does not address recognition and measurement, the Company looked to other accounting literature for guidance where the performance obligation does not fall under ASC 606, and determined that for the Alzheimer's Disease Services, the guidance in ASC 606 should be analogized for the recognition, measurement and reporting of this performance obligation, and for the cost sharing provisions, the Company determined that the guidance in ASC 730, Research and Development should be applied.

The transaction price at inception included upfront fixed consideration of $125.0 million. All potential future milestones and other payments were considered constrained at the inception of the Sanofi Collaboration Agreement since the Company could not conclude it was probable that a significant reversal in the amount recognized would not occur. During the years ended December 31, 2019 and 2018, the transaction price increased by $20.4 million and $2.3 million, respectively, with increases of $10.4 million and $2.3 million, respectively, related to costs incurred for Retained Activities that were no longer constrained. Additionally, the $10.0 million milestone triggered by the commencement of a DNL758 Phase 1 clinical trial in healthy volunteers, as described below, was included in the increase in transaction price for the year ended December 31, 2019.

The respective standalone value for each of the performance obligations has been determined by applying the SSP method and the transaction price allocated based on the relative SSP method with revenue recognition timing to be determined either by delivery or the provision of services.

The Company used an adjusted market assessment approach to estimate the selling price for the program licenses, and an expected cost plus margin approach for estimating the Alzheimer’s Disease Services and the Retained Activities. The program licenses and existing know-how were delivered on the effective date of the Sanofi Collaboration Agreement. The Alzheimer’s Disease Services and the Retained Activities are expected to be delivered over time as the services are performed. For the Alzheimer's Disease Services, revenue will be recognized over time using the input method, based on costs incurred to perform the services, since the level of costs incurred over time is thought to best reflect the transfer of services to Sanofi. For the Retained Activities, revenue will be recognized over time using the output method, based on amounts invoiced to Sanofi, since this is believed to directly correlate to the value of the services performed.

In July 2019, Sanofi commenced a DNL758 Phase 1 clinical trial in healthy volunteers, which triggered a milestone payment of $10.0 million, which the Company received in August 2019. The entire milestone payment was recognized in collaboration revenue in the year ended December 31, 2019. There were no milestones received or recognized in the year ended December 31, 2018.

A contract liability of $3.5 million and $3.9 million was recorded on the Consolidated Balance Sheets as of December 31, 2019 and 2018, respectively. These contract liabilities relate to the portion of the Alzheimer's Disease Services performance obligation yet to be satisfied, with such amounts to be recognized over the estimated period of the services, which is expected to be several years. There was a receivable of $1.2 million and $2.3 million as of December 31, 2019 and 2018, respectively, associated with the Sanofi Collaboration Agreement.

In assessing the Sanofi Collaboration Agreement, management is required to exercise considerable judgment in estimating revenue to be recognized. Management applies judgment in determining the separate performance obligations, in estimating the selling price, in determining when control was transferred to Sanofi for the licenses, and in estimating total future costs when using the input method.

Through December 31, 2019, Denali has received milestone payments of $10.0 million and has not recorded any product sales under the Sanofi Collaboration Agreement.

Takeda

In January 2018, the Company entered into a Collaboration and Option Agreement ("Takeda Collaboration Agreement") with Takeda Pharmaceutical Company Limited ("Takeda"), pursuant to which the Company granted Takeda an option to develop and commercialize, jointly with the Company, certain biologic products that are enabled by Denali's blood-brain barrier ("BBB") delivery technology and intended for the treatment of neurodegenerative disorders. The programs were Denali’s ATV:BACE1/Tau, ATV:TREM2 and PTV:PGRN programs. The Takeda Collaboration Agreement became effective in February 2018, at which time Takeda paid the Company an upfront payment of $40.0 million. Takeda may pay up to an aggregate of $25.0 million with respect to each of the three programs directed to a target and based upon the achievement of certain preclinical milestone events, up to $75.0 million in total, $5.0 million of which was paid upon the Takeda Collaboration Agreement becoming effective. In February 2019, the agreement was amended to replace the ATV:BACE1/Tau program with the ATV:Tau program. The amendment did not have a material impact to the consolidated financial statements.

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

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

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

In addition, if Takeda exercises its option for all three collaboration programs, Takeda may be obligated to pay Denali up to an aggregate of $407.5 million upon achievement of certain clinical milestone events and up to an aggregate of $300.0 million in regulatory milestone events relating to receipt of regulatory approval in the United States, certain European countries and Japan. Takeda may also be obligated to pay Denali up to $75.0 million per biologic product upon achievement of a certain sales-based milestone, or an aggregate of $225.0 million if one biologic product from each program achieves this milestone.

If Takeda exercises its option for a particular target, Denali and Takeda will share equally the development and commercialization costs, and, if applicable, the profits, for each collaboration program.

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

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

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

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

The transaction price at inception included fixed consideration consisting of the upfront fee of $40.0 million, the $15.6 million premium on the sale of common stock, and the first preclinical milestone payment of $5.0 million. It also included variable consideration of $26.0 million relating to future milestones that were not constrained. The amount of variable consideration was estimated using the most likely amount method.

The remaining $44.0 million of preclinical milestones were considered constrained at the inception of the Takeda Collaboration Agreement since the Company could not conclude it is probable that a significant reversal in the amount recognized will not occur. Additionally, cost and profit sharing income, and the development and commercial milestones as outlined above, have not been considered given Takeda has not exercised its options for the development and commercial phases for any program. There was no change in the transaction price during the years ended December 31, 2019 and 2018. This will be reassessed at each reporting period.

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

Revenue is recognized when, or as, the Company satisfies its performance obligations by transferring the promised services to Takeda. Revenue is being recognized over time using the input method, based on costs incurred to perform the research services, since the level of costs incurred over time is thought to best reflect the transfer of services to Takeda. There were no material changes in estimates during the years ended December 31, 2019 and 2018.

A contract liability of $59.0 million and $64.9 million is recorded on the Consolidated Balance Sheets as of December 31, 2019 and 2018, respectively. These contract liabilities relate to the three performance obligations identified, with such amounts to be recognized over the estimated period of the pre-IND research services, which is expected to be several years. There was no receivable as of December 31, 2019, and there was a receivable of $5.0 million as of December 31, 2018, related to the Takeda Collaboration Agreement.

Revenue recognized relating to future milestone payments of $2.4 million and $1.7 million, which the Company concluded is probable that a significant reversal in the amount recognized will not occur, is presented net in the contract liability on the Consolidated Balance Sheets as of December 31, 2019 and 2018, respectively.

In assessing the Takeda Collaboration Agreement, management is required to exercise considerable judgment in estimating revenue to be recognized. Management applies judgment in determining the separate performance obligations in the research period, estimating variable consideration, and estimating total future costs when using the input method.

Through December 31, 2019, Denali has received $15.0 million in preclinical milestone payments from Takeda and has not recorded any product sales under the Takeda Collaboration Agreement.

Collaboration Revenue

Revenue disaggregated by collaboration agreement and performance obligation is as follows (in thousands):

	Year Ended December 31,	
	2019	2018
Takeda Collaboration Agreement[(1)]	$ 5,926	$ 5,677
Sanofi Collaboration Agreement:		
CNS Program License	—	73,932
Peripheral Program License	10,000	47,148
Alzheimer's Disease Services[(1)]	358	60
Retained Activities	10,394	2,343
Total Sanofi Collaboration Revenue	20,752	123,483
Total Collaboration Revenue	$ 26,678	$ 129,160

(1) Amounts for the year ended December 31, 2019 represent revenue recognized that was included in the contract liability balance at the beginning of the year. There was no deferred revenue at the beginning of the year ended December 31, 2018. There was no collaboration revenue in the year ended December 31, 2017.

7. License Agreements

Genentech

In June 2016, the Company entered into an Exclusive License Agreement with Genentech, Inc. ("Genentech"). The agreement gives the Company access to Genentech's LRRK2 inhibitor small molecule program for Parkinson's disease. Under the agreement, Genentech granted the Company (i) an exclusive, worldwide, sublicensable 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, sublicensable license to certain related know-how, in each case, to develop and commercialize certain compounds and licensed products incorporating any such compound.

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. These milestones include up to $37.5 million in clinical milestone payments, $102.5 million in regulatory milestone payments and $175.0 million in commercial milestone payments. In addition, the Company may owe royalties on net sales of licensed products ranging from low to high single-digit percentages.

To date, the Company has paid Genentech $12.5 million in the aggregate, including an upfront fee, a technology transfer fee and a clinical milestone payment, all of which was recorded as research and development expense as incurred. No amounts were recorded in the years ended December 31, 2019 or 2018. The first clinical milestone payment of $2.5 million was recorded as research and development expense during the year ended December 31, 2017.

8. Balance Sheet Components

Property and Equipment, Net

Property and equipment, net consists of the following (in thousands):

	As of December 31,	
	2019	2018
Lab equipment	$ 21,846	$ 14,352
Leasehold improvements	34,563	22,288
Computers equipment and purchased software	1,156	458
Furniture and fixtures	1,440	74
Total property and equipment	59,005	37,172
Less: accumulated depreciation	(12,273)	(12,010)
Total property and equipment, net	$ 46,732	$ 25,162

Depreciation expense was $8.0 million, $7.4 million and $3.1 million for the years ended December 31, 2019, 2018 and 2017, respectively.

Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consists of the following (in thousands):

	As of December 31,	
	2019	2018
Accrued compensation	$ 8,739	$ 9,952
Accrued clinical costs	5,042	2,091
Accrued manufacturing and other research & development costs	5,251	4,179
Accrued general, administrative and shared costs	1,310	2,250
Deferred rent, current	—	616
Operating lease liability, current	3,665	—
Other current liabilities	8	380
Total accrued expenses and other current liabilities	$ 24,015	$ 19,468

9. Commitments and Contingencies

Lease Obligations

In May 2018, the Company entered into an amendment to its operating lease for its former corporate headquarters in South San Francisco (the "Headquarters Lease Amendment") to relocate and expand its headquarters to 148,020 rentable square feet in a building in South San Francisco, California (the "New Premises"). The Headquarters Lease Amendment has a contractual term of ten years from the legal commencement date, which was April 1, 2019 when the building was ready for occupancy. For accounting purposes, the lease commencement date was determined to be August 1, 2018, which was the date at which the Company was deemed to have obtained control over the property. The Company has an option to extend the lease term for a period of ten years by giving the landlord written notice of the election to exercise the option at least nine months, but not more than twelve months, prior to the expiration of the Headquarters Lease Amendment lease term. The Company determined that this renewal was not reasonably certain at lease inception.

The Headquarters Lease Amendment provides for monthly base rent amounts escalating over the term of the lease. In addition, the Headquarters Lease Amendment provided a tenant improvement allowance ("TIA") of up to $25.9 million, which was fully utilized, of which $4.4 million will be repaid to the landlord in the form of additional monthly rent. This is recorded as leasehold improvement assets and an offset to the lease ROU asset on the Consolidated Balance Sheet as of December 31, 2019. The Company is also required to pay the operating expenses for the New Premises, such as taxes and insurance, which are treated as variable lease payments.

As of December 31, 2019, the carrying value of the ROU asset was $33.9 million. The related current and non-current liabilities as of December 31, 2019 were $3.7 million and $68.9 million, respectively. The current and non-current lease liabilities are included in accrued expenses and other current liabilities and operating lease liability, less current portion, respectively, in the Consolidated Balance Sheet.

Management exercised judgment in applying the requirements of ASC 842, including the determination as to whether certain contracts contain a lease and for the Headquarters Lease Amendment, the discount rate used to determine the measurement of the lease liability. As the implicit rate of the Headquarters Lease Amendment was not known, the Company estimated a 9.0% discount rate, which was management’s estimate of the Company’s incremental borrowing rate. To estimate the incremental borrowing rate, management considered observable debt yields of comparable market instruments, as well as benchmarks within the Headquarters Lease Amendment that may be indicative of the rate implicit in the lease.

Total operating lease costs, including variable and short-term lease costs, was $10.2 million for the year ended December 31, 2019. Rent expense excluding amortization of leasehold improvements was $6.0 million and $2.2 million for the years ended December 31, 2018 and 2017, respectively.

Operating lease liabilities are calculated as the net present value of the remaining lease payments over the remaining lease term. In determining the present value of lease payments, we use our incremental borrowing rate based on the information available at the lease commencement date. As of December 31, 2019, the weighted average remaining lease term is 9.3 years and the weighted average discount rate used to determine the operating lease liability was 9.0%. Cash paid for amounts included in the measurement of lease liabilities for the year ended December 31, 2019 was $5.4 million and was included in net cash used in operating activities in our Consolidated Statements of Cash Flows.

The following table reconciles the undiscounted cash flows for the next five years and total of the remaining years to the operating lease liabilities recorded in the Consolidated Balance Sheet as of December 31, 2019 (in thousands):

Year Ended December 31:		
2020	$	9,737
2021		10,391
2022		10,731
2023		11,083
2024		11,447
Thereafter		54,074
Total undiscounted lease payments		107,463
Present value adjustment		(34,933)
Net operating lease liabilities	$	72,530

In October 2018, the Company entered into a sublease agreement ("Sublease Agreement") to sublease approximately 36,835 rentable square feet of space in its New Premises. The Sublease Agreement has a term of five years from the commencement date of April 12, 2019 and provides for the Company to receive monthly base rent amounts escalating over the term of the lease. The Company also passes through a portion of the operating expenses, such as taxes and insurance for the New Premises to the sublessee, which are treated as variable sublease income. Total sublease income, including rent and variable sublease cost reimbursements, was $2.6 million for the year ended December 31, 2019. There was no sublease income for the years ended December 31, 2018 or 2017.

The following table details the future undiscounted cash inflows relating to the Company's Sublease Agreement as of December 31, 2019 (in thousands):

Year Ended December 31:		
2020	$	2,842
2021		2,925
2022		3,009
2023		3,096
2024		876
Thereafter		—
Total undiscounted sublease receipts	$	12,748

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 Consolidated Balance Sheets, Consolidated Statements of Operations and Comprehensive Loss, or Consolidated Statements of Cash Flows.

Commitments

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

As of December 31, 2019 and 2018, the Company had open non-cancellable purchase orders for biological product development and manufacturing costs totaling $21.2 million and $24.7 million, respectively. The activities under these purchase orders are expected to be completed by November 2024. As of December 31, 2019 and 2018, the Company had total non-refundable purchase commitments of $11.2 million and $14.0 million, respectively, under the DMSA.

During the years ended December 31, 2019 and 2018, the Company incurred costs of $12.7 million and $3.9 million, and made payments of $12.5 million and $3.4 million, respectively, for the development and manufacturing services rendered under the DMSA. The Company had not incurred any costs or made any payments for the development and manufacturing services rendered under the DMSA for the year ended December 31, 2017.

In the normal course of business, the Company enters into various firm purchase commitments primarily related to research and development activities. The Company had contractual obligations under license and other agreements of $1.1 million and $1.2 million as of December 31, 2019 and 2018, respectively.

10. Convertible Preferred Stock

The Company entered into a preferred stock purchase agreement (“Preferred Stock Purchase Agreement”), with certain investors in May 2015 (the “Initial Closing”), under which the Company agreed to sell up to 45,223,970 shares of Series A-1 convertible preferred stock and 4,361,530 shares of Series A-2 convertible preferred stock. Additionally, at the Initial Closing, the Company concurrently issued 6,295,810 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.

In May 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 in July 2015 (“Second Additional Closing”), the Company issued an additional 2,420,830 shares of Series A-1 convertible preferred stock for net proceeds of $9.6 million.

In January 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, and also issued 11,250,000 shares of Series A-1 convertible preferred stock (the “first Tranche Closing”), for net proceeds of $45.0 million. In June 2016 (the “Second Tranche Closing and Series A-2 Closing”), the Company issued 22,166,550 shares of Series A-1 convertible preferred stock and 4,361,530 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.

In June 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 7,646,240 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 81,787,360 shares and the authorized shares of its preferred stock to 63,288,470 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.

In August 2016, (the “Second Series B-1 Closing”), the Company sold 478,120 shares of Series B-1 convertible preferred stock at a price of $16.00 per share for net proceeds of $7.6 million.

In November 2017, the Company sold 1,764,710 shares of Series B-2 convertible preferred stock at a price of $17.00 per share for net proceeds of $29.9 million.

Prior to the conversion of the convertible preferred stock upon closing of the IPO, the rights, preferences and privileges of the convertible preferred stock were as follows:

Dividend Rights

The holders of preferred stock were 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, $0.32 per share per annum for Series B-1, and $0.34 per share per annum for Series B-2, from and after the date of issuance of such shares. As of December 31, 2016, and through the date of conversion, no such dividends were declared or accrued.

Dividends on any other class of capital stock could not be paid unless the holders of the preferred stock first received, or simultaneously received, the preferred stock dividend. The holders of preferred stock also participated in dividends paid on common stock as if the shares of preferred stock had been converted into shares of common stock and were considered participating securities.

Conversion Rights

The holders of preferred stock had right to convert at any time into shares of common stock initially at a one-for-one ratio. All shares of the preferred stock would have been 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 was 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 were entitled to be paid out of the assets of the Company available for distribution to its stockholders, before any payment could have been 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 were insufficient to pay holders of Preferred Stock the full amount they are entitled to, the holders of preferred stock would have shared 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 would have been 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 classified its convertible preferred stock outside of stockholders' deficit as certain change in control events are outside the Company's control.

Redemption

Upon certain change in control events that were outside of the Company's control, including liquidation, sale or transfer of control of the Company, holders of the convertible preferred stock could have caused its redemption. Shares of preferred stock could have been 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 could have been 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 could have redeemed 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.

Voting Rights

Each share of preferred stock had voting rights equal to the number of shares of common stock into which the preferred stock could have been converted immediately after the close of business on the record date.

As long as certain investors in Series A convertible preferred stock held 100,000 or more shares of convertible preferred stock purchased pursuant to the Preferred Stock Purchase Agreement, they were entitled to elect individually one member of the Board totaling five Series A Directors. Series B convertible preferred stockholders were 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 were entitled to elect two additional members of the Board that were not otherwise an affiliate of the Company or of any investor.

Upon the closing of the IPO, all outstanding shares of convertible preferred stock converted into 60,365,020 shares of common stock. As of December 31, 2019 and 2018, the Company did not have any convertible preferred stock issued or outstanding.

11. Stock-Based Awards

2017 Equity Incentive Plan

In December 2017, the Company adopted the 2017 Equity Incentive Plan (the “2017 Plan”), which initially reserved approximately 6.4 million shares of common stock for the issuance of stock options, restricted stock and other stock awards, to employees, non-employee directors, and consultants under terms and provisions established by the Board of Directors and approved by the stockholders. The 2017 Plan provides that the number of shares reserved and available for issuance under the 2017 Plan will automatically increase each January 1, beginning on January 1, 2019, by the least of (i) 10.0 million shares, (ii) 5% of the outstanding shares on the last day of the immediately preceding fiscal year, or (iii) such number of shares determined by the administrator of the 2017 Plan. In January 2019, common stock available for issuance under the 2017 Plan was increased by approximately 4.8 million shares as a result of this automatic increase provision.

Awards granted under the 2017 Plan expire no later than ten years from the date of grant. For stock options, the option price shall not be less than 100% of the estimated fair value of the Company's common stock on the day of grant. Options granted typically vest over a four-year period but may be granted with different vesting terms.

2015 Stock Incentive Plan

In May 2015, the Company adopted the 2015 Stock Incentive Plan (the “2015 Plan”), which as amended, reserved approximately 8.3 million shares of common stock for the issuance of stock options, restricted stock and other stock awards, to employees, non-employee directors, and consultants under terms and provisions established by the Board of Directors and approved by the stockholders. Awards granted under the 2015 Plan expire no later than ten years from the date of grant. For stock options, the option price shall not be less than 100% of the estimated fair value of the Company's common stock on the day of grant. Options granted typically vest over a four-year period but may be granted with different vesting terms.

Upon adoption of the 2017 Plan, no new awards or grants are permitted under the 2015 Plan, and the approximately 0.2 million shares that were then unissued and available for future award under the 2015 Plan became available under the 2017 Plan. The 2015 Plan will continue to govern restricted stock awards and option awards previously granted thereunder.

As of December 31, 2019 and 2018, there were approximately 3.4 million and 2.3 million common shares available for the Company to grant under the 2017 Plan, respectively.

Stock Option Activity

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

	Number of Options	Weighted-Average Exercise Price	Weighted-Average remaining contractual life (years)	Aggregate Intrinsic Value (in thousands)
Balance at December 31, 2018	9,612,652	$ 10.49	8.20	$ 97,804
Options granted	3,610,835	18.58		
Options exercised	(786,638)	4.27		
Options forfeited	(796,115)	16.72		
Balance at December 31, 2019	11,640,734	$ 12.96	7.79	$ 51,879
Options vested and expected to vest at December 31, 2019	9,896,002	$ 15.13	8.17	$ 22,672
Options exercisable at December 31, 2019	3,938,523	$ 11.19	7.38	$ 24,552

Aggregate intrinsic value represents the difference between the fair value of the Company's common stock and the exercise price of outstanding options. The total intrinsic value of options exercised was $13.1 million, $9.8 million and $3.5 million for the years ended December 31, 2019, 2018 and 2017, respectively. During the years ended December 31, 2019, 2018, and 2017 the weighted-average grant-date fair value of the options vested was $10.09, $3.85, and $1.94 per share, respectively. The weighted-average grant date fair value of all options granted during the years ended December 31, 2019, 2018 and 2017 was $11.86, $14.79, and $6.41 per share, respectively.

Stock Options Granted to Employees with Service-Based Vesting

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

	Year Ended December 31,		
	2019	2018	2017
Expected term (in years)	5.50 - 6.08	5.50 - 6.08	6.08
Volatility	65.5% - 77.8%	79.4% - 87.4%	81.9% - 91.3%
Risk-free interest rate	1.5% - 2.6%	2.6% - 3.1%	1.8% - 2.3%
Dividend yield	—	—	—

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

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

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

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

Performance and Market Contingent Stock Options Granted to Employees

In August and November 2015, the Board of Directors granted approximately 1.6 million and 0.1 million shares 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.

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. In the event that neither of these market triggers are achieved by the specified timelines, such awards will terminate with respect to that portion of the shares. The expense recognized associated with these performance- and market- contingent awards was $5.2 million and $0.5 million of general and administrative and research and development expense, respectively, during the year ended December 31, 2019. The remaining expense for these awards, to be recognized using the accelerated attribution method, is $0.3 million, which will be recognized over the remaining derived service period of approximately nine months.

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

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

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

Restricted Stock Activity

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

Aggregated information regarding RSAs and RSUs granted under the Plan for the year ended December 31, 2019 is summarized below:

	Share Awards & Units	Weighted-Average Fair Value at Date of Grant per Share
Unvested at December 31, 2018	503,243	$ 4.86
Granted	850,234	18.86
Vested and released	(419,064)	2.63
Forfeited	(51,777)	20.50
Unvested at December 31, 2019	882,636	$ 18.67
Expected to vest – December 31, 2019	882,636	$ 18.67

The aggregate intrinsic value of RSUs is calculated as the closing price per share of the Company's common stock on the last trading day of the fiscal period, multiplied by the number of RSUs expected to vest. The total intrinsic value of RSUs expected to vest was $15.4 million as of December 31, 2019. During the year ended December 31, 2018, the weighted-average grant-date fair value of RSUs granted was $15.92. No RSAs or RSUs were granted in the year ended December 31, 2017. The total fair value of RSAs and RSUs that vested during the years ended December 31, 2019, 2018, and 2017 (measured on the date of vesting) was $8.8 million, $37.0 million and $14.3 million, respectively. There was $13.7 million of total unrecognized stock-based compensation related to unvested RSUs at December 31, 2019, all of which is expected to be recognized over a remaining weighted-average period of 3.2 years.

Employee Stock Purchase Plan

In December 2017, the Company adopted the 2017 Employee Stock Purchase Plan (the “2017 ESPP”), which initially reserved 1.0 million shares of common stock for employee purchases under terms and provisions established by the Board of Directors. The 2017 ESPP provides that the number of shares reserved and available for issuance under the 2017 ESPP will automatically increase each January 1, beginning on January 1, 2019, by the least of (i) 2.0 million shares, (ii) 1% of the outstanding shares on the last day of the immediately preceding fiscal year, or (iii) such number of shares determined by the administrator of the 2017 Plan. In January 2019, common stock available for issuance under the 2017 ESPP was increased by approximately 1.0 million shares as a result of this automatic increase provision.

Under the 2017 ESPP, employees may purchase common stock through payroll deductions at a price equal to 85% of the lower of the fair market value of common stock on the first trading day of each offering period or on the exercise date. The 2017 ESPP provides for consecutive, overlapping 12-month offering periods. The offering periods are scheduled to start on the first trading day on or after May 31 or November 30 of each year, except for the first offering period which commenced on December 8, 2017, the first trading day after the effective date of the Company’s registration statement. Contributions under the 2017 ESPP are limited to a maximum of 15% of an employee's eligible compensation. We issued 0.2 million and 0.1 million shares of common stock under the 2017 ESPP during the years ended December 31, 2019 and 2018, respectively.

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

	Year Ended December 31,		
	2019	2018	2017
Expected term (in years)	0.50 - 1.00	0.50 - 1.00	0.48 - 0.98
Volatility	47.6% - 59.1%	61.0% - 64.3%	50.0% - 51.3%
Risk-free interest rate	1.6% - 2.4%	2.1% - 2.7%	1.5% - 1.7%
Dividend yield	—	—	—

Stock-Based Compensation Expense

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

	Year Ended December 31,		
	2019	2018	2017
Research and development	$ 19,261	$ 10,093	$ 2,852
General and administrative	19,117	8,698	1,557
Total	$ 38,378	$ 18,791	$ 4,409

As of December 31, 2019, total unamortized stock-based compensation expense related to employee and non-employee awards was $76.2 million. The weighted-average period over which such stock-based compensation expense will be recognized is approximately 2.7 years.

12. Defined Contribution Plan

The Company sponsors a 401(k) retirement savings plan for the benefit of its employees, including Denali's 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. The Company made contributions to the Plan for eligible participants, and recorded contribution expenses of $1.6 million, $0.9 million and $0.5 million for the years ended December 31, 2019, 2018, and 2017, respectively.

13. Income Taxes

The Company has reported pre-tax operating losses for all periods presented. The Company has not reflected any benefit for corresponding tax net operating loss carryforwards in the accompanying consolidated 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, 2019, 2018, and 2017 is different from the federal statutory tax rate primarily due to the valuation allowance against deferred tax assets. The Company's effective tax rate differs from the federal statutory rate as follows:

	Year Ended December 31,		
	2019	2018	2017
Taxes at the U.S. statutory tax rate	21.0 %	21.0 %	34.0 %
Effect of Tax Act	—	—	(26.6)
Change in valuation allowance	(24.4)	(20.7)	(7.3)
Research tax credits	3.5	10.2	1.0
Stock-based compensation	0.1	(0.7)	(1.0)
Nondeductible acquisition-related costs	—	(9.5)	—
Other	(0.1)	(0.3)	(0.1)
Total provision for income taxes	0.1 %	— %	— %

The components of the Company's net deferred tax assets are as follows (in thousands):

	December 31,	
	2019	2018
Deferred tax assets:		
Net operating loss carryforwards	$ 56,612	$ 35,023
Tax credit carryforwards	19,133	9,565
Contract liabilities	13,516	—
Operating lease liability	15,686	—
Stock-based compensation	9,513	3,305
Accruals and other	11,815	17,181
Gross deferred tax assets	126,275	65,074
Valuation allowance	(112,713)	(60,915)
Net deferred tax assets	13,562	4,159
Deferred tax liabilities:		
Property and equipment	(6,225)	(4,159)
Operating lease right-of-use asset	(7,337)	—
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, 2019 and 2018. There was an increase in the net valuation allowance of $51.8 million during the year ended December 31, 2019.

As of December 31, 2019, the Company has federal net operating loss ("NOL") carryforwards of approximately $221.5 million, which are available to reduce future taxable income, and has federal R&D and orphan drug tax credits of approximately $14.5 million and $1.7 million respectively, both of 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 $144.2 million, which are available to reduce future taxable income, and has state tax credits of approximately $9.8 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. Annual limitations may result in expiration of net operating loss and tax credit carryforwards before some or all of such amounts have been utilized.

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,		
	2019	2018	2017
Unrecognized tax benefits at January 1	$ 2,642	$ 1,146	$ 531
Additions for tax positions taken in a prior year	107	—	—
Additions for tax positions taken in the current year	2,595	1,506	640
Reductions for tax positions taken in the prior year	(45)	(10)	(25)
Unrecognized tax benefits at December 31	$ 5,299	$ 2,642	$ 1,146

If recognized, none of the unrecognized tax benefits 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, 2019, 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.

14. Net Loss and Net Loss Per Share

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 as the inclusion of all potential dilutive securities 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:

	Year Ended December 31,		
	2019	2018	2017
Options issued and outstanding and ESPP shares issuable	11,921,434	9,789,594	6,835,313
Restricted shares subject to future vesting	882,636	503,243	2,293,788
Early exercised common stock subject to future vesting	—	135,424	369,796
Total	12,804,070	10,428,261	9,498,897

15. Subsequent event

In January 2020, the Company sold 9.0 million shares of common stock (inclusive of shares sold pursuant to an overallotment option granted to the underwriters in connection with the offering) through an underwritten public offering at a price of $23.00 per share for aggregate net proceeds of approximately $194.1 million.

16. Selected Quarterly Financial Data (Unaudited)

The following tables provide the selected quarterly financial data for the years ended December 31, 2019 and 2018 (in thousands, except per share amounts):

	Quarter Ended			
	December 31, 2019	September 30, 2019	June 30, 2019	March 31, 2019
Collaboration revenue	$ 4,672	$ 13,604	$ 4,197	$ 4,205
Loss from operations	(57,758)	(50,155)	(62,763)	(42,508)
Net loss	(54,025)	(46,260)	(58,337)	(38,992)
Net loss per share, basic and diluted[1]	$ (0.56)	$ (0.48)	$ (0.61)	$ (0.41)

[1] Basic and diluted net income per share for the quarter ended December 31, 2019 is calculated using 96,078,950 shares.

	Quarter Ended			
	December 31, 2018	September 30, 2018	June 30, 2018	March 31, 2018
Collaboration revenue	$ 125,676	$ 1,195	$ 1,648	$ 641
Income (loss) from operations	74,722	(37,964)	(57,382)	(25,748)
Net income (loss)	77,533	(35,371)	(54,724)	(23,678)
Net income (loss) per share, basic[1]	$ 0.82	$ (0.38)	$ (0.59)	$ (0.26)
Net income (loss) per share, diluted[1]	$ 0.79	$ (0.38)	$ (0.59)	$ (0.26)

[1] Basic and diluted net income per share for the quarter ended December 31, 2018 is calculated using 94,299,096 and 97,746,224 shares, respectively, the latter of which is computed by giving effect to all dilutive potential ordinary shares including options.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

None.

ITEM 9A. CONTROLS AND PROCEDURES

Conclusions Regarding the Effectiveness of Disclosure Controls and Procedures

As of December 31, 2019, management, with the participation of our Chief Executive Officer and Chief Financial Officer, performed an evaluation of the effectiveness of the design and operation of our disclosure controls and procedures as defined in Rules 13a-15(e) and 15d-15(e) of the Exchange Act. Our disclosure controls and procedures are designed to ensure that information required to be disclosed in the reports we file or submit under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including the Chief Executive Officer and the Chief Financial Officer, to allow timely decisions regarding required disclosures.

Any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objective and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that, as of December 31, 2019, the design and operation of our disclosure controls and procedures were effective at a reasonable assurance level.

Changes in Internal Control over Financial Reporting

There was no change in our internal control over financial reporting identified in connection with the evaluation required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the quarter ended December 31, 2019 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Management's Annual Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting (as defined in Rule 13a-15(f) under the Exchange Act). Under the supervision of and with the participation of our principal executive officer and principal financial officer, our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2019 based on the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in "Internal Control—Integrated Framework" (2013). Based on this assessment, management concluded that our internal control over financial reporting was effective as of December 31, 2019.

The effectiveness of our internal control over financial reporting as of December 31, 2019 has been audited by Ernst & Young LLP, an independent registered public accounting firm, as stated in their report which is included herein.

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Denali Therapeutics Inc.

Opinion on Internal Control Over Financial Reporting

We have audited Denali Therapeutics Inc.'s internal control over financial reporting as of December 31, 2019, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (2013 framework) (the COSO criteria). In our opinion, Denali Therapeutics Inc. (the Company) maintained, in all material respects, effective internal control over financial reporting as of December 31, 2019, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States) (PCAOB), the consolidated balance sheets of the Company as of December 31, 2019 and 2018, the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders' equity (deficit) and cash flows for each of the three years in the period ended December 31, 2019, and the related notes and our report dated February 27, 2020 expressed an unqualified opinion thereon.

Basis for Opinion

The Company's management is responsible for maintaining effective internal control over financial reporting and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Annual Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the Company's internal control over financial reporting based on our audit. We are a public accounting firm registered with the PCAOB and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audit in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether effective internal control over financial reporting was maintained in all material respects.
Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

Definition and Limitations of Internal Control Over Financial Reporting

A company's 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 generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

/s/ Ernst & Young LLP

Redwood City, California
February 27, 2020

ITEM 9B. OTHER INFORMATION

None.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

Information required by this item will be contained in our definitive proxy statement to be filed with the SEC on Schedule 14A in connection with our 2020 Annual Meeting of Stockholders (the “Proxy Statement”), which is expected to be filed not later than 120 days after December 31, 2019, and is incorporated herein by reference.

ITEM 11. EXECUTIVE COMPENSATION

Information required by this item will be contained in the Proxy Statement and is incorporated herein by reference.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

Information required by this item will be contained in the Proxy Statement and is incorporated herein by reference.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS AND DIRECTOR INDEPENDENCE

Information required by this item will be contained in the Proxy Statement and is incorporated herein by reference.

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES

Information required by this item will be contained in the Proxy Statement and is incorporated herein by reference.

PART IV

ITEM 15. EXHIBITS AND FINANCIAL STATEMENT SCHEDULES

(a) The following documents are filed as part of this report:

1. Financial Statements

   See Index to Financial Statements in Part II Item 8 of this Annual Report on Form 10-K.

2. Financial Statement Schedules

   All schedules are omitted because they are not applicable or the required information is shown in the financial statements or notes thereto.

3. Exhibits

   The documents listed in the Exhibit Index are incorporated by reference or are filed with this report, in each case as indicated therein (numbered in accordance with Item 601 of Regulation S-K).

EXHIBIT INDEX

Exhibit Number	Description	Incorporated by Reference			
		Form	File No.	Number	Filing Date
3.1	Amended and Restated Certificate of Incorporation of the Registrant.	8-K	001-38311	3.1	12/12/2017
3.2	Amended and Restated Bylaws of the Registrant.	8-K	001-38311	3.2	12/12/2017
4.1	Investors' Rights Agreement among the Registrant and certain of its stockholders, dated May 8, 2015, as amended on June 4, 2015, July 22, 2015 and June 22, 2016.	S-1	333-221522	4.1	11/13/2017
4.2	Specimen common stock certificate of the Registrant.	S-1/A	333-221522	4.2	11/27/2017
4.3	Description of the registrant's common stock.	—	—	—	Filed herewith
10.1+	Form of Indemnification Agreement between the Registrant and each of its directors and executive officers.	S-1/A	333-221522	10.1	11/27/2017
10.2+	2015 Stock Incentive Plan, as amended, and forms of agreement thereunder.	S-1	333-221522	10.2	11/13/2017
10.3+	2017 Equity Incentive Plan and forms of agreements thereunder.	S-1/A	333-221522	10.3	11/27/2017
10.4+	2017 Employee Stock Purchase Plan and form of agreement thereunder.	S-1/A	333-221522	10.4	12/7/2017
10.5+	Offer Letter between the Registrant and Ryan J. Watts, Ph.D., dated November 10, 2017.	S-1	333-221522	10.5	11/13/2017
10.6+	Offer Letter between the Registrant and Alexander O. Schuth, M.D., dated November 10, 2017.	S-1	333-221522	10.6	11/13/2017
10.7+	Offer Letter between the Registrant and Steve E. Krognes, dated November 10, 2017.	S-1	333-221522	10.7	11/13/2017
10.8+	Offer Letter between the Registrant and Carole Ho, M.D., dated November 10, 2017.	S-1	333-221522	10.8	11/13/2017
10	Lease Agreement between the Registrant and HCP Oyster Point III LLC, dated September 24, 2015.	S-1	333-221522	10.9	11/13/2017
10.10Ü	Exclusive License Agreement between the Registrant and Genentech, Inc., dated June 17, 2016.	S-1	333-221522	10.10	11/13/2017
10.11Ü	License and Collaboration Agreement between the Registrant, F-star Gamma Limited, F-star Biotechnologische Forschungs-und Entwicklungsges m.b.H. and F-star Biotechnology Limited, dated August 24, 2016.	S-1	333-221522	10.11	11/13/2017
10.12Ü	Development and Manufacturing Services Agreement between the Registrant and Lonza Sales AG, dated September 6, 2017, as amended by Amendment No. 1 on October 18, 2017.	S-1	333-221522	10.12	11/13/2017
10.12.1#	Amendment No. 2 to Development and Manufacturing Services Agreement between the Registrant and Lonza Sales AG, dated September 6, 2017, as amended by Amendment No. 1 on October 18, 2017, dated January 18, 2018.	10-K	001-38311	10.12.1	3/19/2018

10.13+	Key Executive Change in Control and Severance Plan.	S-1	333-221522	10.13	11/13/2017
10.14+	Executive Incentive Compensation Plan.	S-1	333-221522	10.14	11/13/2017
10.15+	Outside Director Compensation Policy.	S-1	333-221522	10.15	11/13/2017
10.16#	Option and Collaboration Agreement between the Registrant and Takeda Pharmaceutical Company Limited, dated January 3, 2018.	10-K/A	001-38311	10.1	7/13/2018
10.17	Common Stock Purchase Agreement between the Registrant and Takeda Pharmaceutical Company Limited, dated January 3, 2018.	10-K	001-38311	10.17	3/19/2018
10.18	Standstill and Stock Restriction Agreement between the Registrant and Takeda Pharmaceutical Company Limited, dated February 23, 2018.	10-K	001-38311	10.18	3/19/2018
10.19	First Amendment to Lease Agreement between the Registrant and HCP Oyster Point III LLC, dated May 2, 2018.	10-Q	001-38311	10.1	8/9/2018
10.20Ü	Amended and Restated Gamma IP License Agreement between the Registrant and F-star Gamma Limited, dated August 24, 2016	10-Q/A	001-38311	10.2	12/6/2018
10.21Ü	Side Letter between the Registrant and F-star Gamma Limited, dated May 21, 2018	10-Q	001-38311	10.3	8/9/2018
10.22Ü	Share Purchase Agreement between the Registrant and F-star Gamma Limited, dated May 30, 2018	10-Q/A	001-38311	10.4	12/6/2018
10.23	Amendment No. 3 to Development and Manufacturing Services Agreement between the Registrant and Lonza Sales AG, dated September 6, 2017, as amended by Amendment No. 1 on October 18, 2017 and Amendment No. 2 dated January 18, 2018	10-Q	001-38311	10.1	11/8/2018
10.24	Amendment No. 4 to Development and Manufacturing Services Agreement between the Registrant and Lonza Sales AG, dated September 6, 2017, as amended by Amendment No. 1 on October 18, 2017 and Amendment No. 2 dated January 18, 2018, and Amendment No. 3 dated November 8, 2018	10-Q	001-38311	10.2	11/8/2018
10.25#	Collaboration and License Agreement between registrant and Genzyme Corporation ("Sanofi"), dated October 29, 2018	10-K	001-38311	10.25	3/12/2019
21.1	Subsidiaries of the Registrant	—	—	—	Filed herewith
23.1	Consent of Independent Registered Public Accounting Firm.	—	—	—	Filed herewith
31.1	Certification of Chief Executive Officer pursuant to Section 302 of the Sarbanes-Oxley Act.	—	—	—	Filed herewith
31.2	Certification of Chief Financial Officer pursuant to Section 302 of the Sarbanes-Oxley Act.	—	—	—	Filed herewith
32.1*	Certification of Chief Executive Officer pursuant to Section 906 of the Sarbanes-Oxley Act.	—	—	—	Furnished herewith
32.2*	Certification of Chief Financial Officer pursuant to Section 906 of the Sarbanes-Oxley Act.	—	—	—	Furnished herewith

101	The following materials from the Company’s Annual Report on Form 10-K for the year ended December 31, 2019, formatted in Inline XBRL: (i) Consolidated Balance Sheets, (ii) Consolidated Statements of Operations and Comprehensive Loss, (iii) Consolidated Statements of Cash Flows (iv) Consolidated Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit) and (v) Notes to Consolidated Financial Statements.	—	—	—	Filed herewith
104	The cover page from the Company's Annual Report on Form 10-K for the year ended December 31, 2019, formatted in Inline XBRL (contained in Exhibit 101)	—	—	—	Filed herewith

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

Ü Portions of the exhibit have been omitted pursuant to an order granted by the Securities and Exchange Commission for confidential treatment.

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

\+ Indicates management contract or compensatory plan.

ITEM 16. FORM 10-K SUMMARY

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this Annual Report on Form 10-K to be signed on its behalf by the undersigned, thereunto duly authorized.

DENALI THERAPEUTICS INC.

Date:	February 27, 2020	By:	/s/ Ryan J. Watts
			Ryan J. Watts, Ph.D.
			President and Chief Executive Officer

POWER OF ATTORNEY

Each person whose signature appears below constitutes and appoints Ryan J. Watts, Ph.D. and Steve E. Krognes, and each of them acting individually, as his or her true and lawful attorney-in-fact and agent, with full power of substitution and resubstitution, for him or her and in his or her name, place and stead, in any and all capacities, to sign any and all amendments to this Annual Report on Form 10-K, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or any of them, or their or his substitutes, may lawfully do or cause to be done by virtue thereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated:

Signature	Title	Date
/s/ Ryan J. Watts Ryan J. Watts, Ph.D.	President, Chief Executive Officer and Director *(Principal Executive Officer)*	February 27, 2020
/s/ Steve E. Krognes Steve E. Krognes	Chief Financial Officer and Treasurer *(Principal Financial and Accounting Officer)*	February 27, 2020
/s/ Vicki Sato Vicki Sato, Ph.D.	Chairperson of our Board of Directors	February 27, 2020
/s/ Marc Tessier-Lavigne Marc Tessier-Lavigne, Ph.D.	Director	February 27, 2020
/s/ Douglas Cole Douglas Cole, M.D.	Director	February 27, 2020
/s/ Jennifer Cook Jennifer Cook	Director	February 27, 2020
/s/ Jay Flatley Jay Flatley	Director	February 27, 2020
/s/ Peter Klein Peter Klein	Director	February 27, 2020
/s/ Robert Nelsen Robert Nelsen	Director	February 27, 2020
/s/ David Schenkein David Schenkein, M.D.	Director	February 27, 2020

DESCRIPTION OF THE REGISTRANT'S SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934

The following summary describes our common stock and preferred stock, as well as certain provisions of our amended and restated certificate of incorporation and amended and restated bylaws. This summary does not purport to be complete and is qualified in its entirety by the provisions of our amended and restated certificate of incorporation and amended and restated bylaws, copies of which have been filed as exhibits to this Annual Report on Form 10-K, as well as to the applicable provisions of the Delaware General Corporation Law.

Authorized Capital Stock

Our authorized capital stock consists of 400,000,000 shares of common stock, par value $0.01 per share, and 40,000,000 shares of preferred stock, par value $0.01 per share. All outstanding shares of common stock are fully paid and non-assessable.

Common Stock

Our common stock is listed on the Nasdaq Global Select Market under the symbol “DNLI.” The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company, LLC. The transfer agent and registrar's address is 6201 15th Avenue, Brooklyn, New York 11219.

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.

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.

Preferred Stock

Under the terms of our amended and restated certificate of incorporation, our board of directors is authorized 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 designations, powers, preferences and rights, and the qualifications, limitations or restrictions thereof, of any wholly unissued series of Preferred Stock, including, without limitation, authority to fix by resolution or resolutions the dividend rights, dividend rate, conversion rights, voting rights, rights and terms of redemption (including sinking fund provisions), redemption price or prices, and liquidation preferences of any such series, and the number of shares constituting any such series and the designation thereof, or any of the foregoing.

The issuance of shares of preferred stock will affect, and may adversely affect, the rights of holders of common stock. It is not possible to state the actual effect of the issuance of any shares of preferred stock on the rights of holders of common stock until our board of directors determines the specific rights attached to that preferred stock. The effects of issuing additional preferred stock could include one or more of the following:

- restricting dividends on the common stock;
- diluting the voting power of the common stock;
- impairing the liquidation rights of the common stock; or
- delaying or preventing changes in control or management of our Company.

Preferred stock will be fully paid and nonassessable upon issuance.

Registration Rights of Certain Stockholders

Certain of our stockholders have registration rights under the investors' rights agreement, as amended (the "**Investor's Rights Agreement**"), by and among us and such stockholders. One of our other stockholders, Takeda Pharmaceutical Company Limited ("**Takeda**"), also has registration rights under the standstill and stock restriction agreement between us and Takeda (the "**Takeda Standstill Agreement**"). These stockholders (and certain of their permitted transferees) may request that the we file registration statements under the Securities Act of 1933 and, upon such request and subject to certain conditions, the Company will be required to use its commercially reasonable efforts to effect any such registration. The Company is generally obligated to bear the expenses, other than underwriting discounts and sales commissions, of all of these registrations. This summary does not purport to be complete and is qualified in its entirety by the provisions of the Investors' Rights Agreement and the Takeda Standstill Agreement, copies of which have been filed as exhibits to this Annual Report on Form 10-K.

Effect of Certain Provisions of our Amended and Restated Certificate of Incorporation and Bylaws and the Delaware Anti-Takeover Statute

Some provisions of Delaware law and our amended and restated certificate of incorporation and amended and restated bylaws contain provisions that could make the following transactions more difficult:

- acquisition of us by means of a tender offer;
- acquisition of us by means of a proxy contest or otherwise; or
- removal of our incumbent officers and directors.

Those provisions, summarized below, are expected to discourage coercive takeover practices and inadequate takeover bids and to promote stability in our management. These provisions are also designed to encourage persons seeking to acquire control of us to first negotiate with our board of directors.

Amended and Restated Certificate of Incorporation and Amended and Restated Bylaws

Classified Board of Directors

Our amended and restated certificate of incorporation provides that our board of directors is divided into three classes, designated Class I, Class II, and Class III. Each class is 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 directors in each class are elected to serve for a three-year term, one class being elected each year by our stockholders. At each annual meeting of stockholders, 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 provides 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

Vacancies and newly created directorships on our board of directors may be filled only by the affirmative vote of a majority of the remaining directors then in office, even though less than a quorum of the board of directors.

No Cumulative Voting

Our amended and restated certificate of incorporation provides 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 provides 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.

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 Delaware General Corporation Law . 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 certain provisions, including those listed above, which would require the approval of a two-thirds majority of our then outstanding common stock. Additionally, our amended and restated certificate of incorporation provides 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 are 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 our Company by means of a proxy contest, tender offer, merger or otherwise.

Delaware Anti-Takeover Statute

We are subject to the provisions of Section 203 of the Delaware General Corporation Law regulating corporate takeovers. In general, Section 203 prohibits a publicly-held Delaware corporation from engaging, under certain circumstances, in a business combination with an interested stockholder for a period of three years following the date the person became an interested stockholder unless:

- prior to the date of the transaction, the board of directors of the corporation approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;

- upon completion of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the voting stock outstanding, but not for determining the outstanding voting stock owned by the interested stockholder, (i) shares owned by persons who are directors and also officers, and (ii) shares owned 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

- at or subsequent to the date of the transaction, the business combination is approved by the board of directors of the corporation and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66-2/3% of the outstanding voting stock which is not owned by the interested stockholder.

Generally, a business combination includes a merger, asset or stock sale, or other transaction resulting in a financial benefit to the interested stockholder. An interested stockholder is a person who, together with affiliates and associates, owns or, within three years prior to the determination of interested stockholder status, did own 15% or more of a corporation’s outstanding voting stock.

Exhibit 21.1

SUBSIDIARIES

Subsidiary Name	Jurisdiction of Incorporation or Organization
Denali BBB Holding Limited	United Kingdom

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the following Registration Statements:

1. Registration Statement (Form S-3 No. 333-230232) of Denali Therapeutics Inc.,
2. Registration Statement (Form S-8 No. 333-230223) pertaining to the 2017 Equity Incentive Plan and 2017 Employee Stock Purchase Plan of Denali Therapeutics Inc., and
3. Registration Statement (Form S-8 No. 333-221946) pertaining to the 2017 Equity Incentive Plan, the 2017 Employee Stock Purchase Plan and the 2015 Stock Incentive Plan of Denali Therapeutics Inc.;

of our reports dated February 27, 2020, with respect to the consolidated financial statements of Denali Therapeutics Inc. and the effectiveness of internal control over financial reporting of Denali Therapeutics Inc. included in this Annual Report (Form 10-K) of Denali Therapeutics Inc. for the year ended December 31, 2019.

/s/ Ernst & Young LLP

Redwood City, California
February 27, 2020

Exhibit 31.1

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

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

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

Date: February 27, 2020

/s/ Ryan J. Watts
Ryan J. Watts, Ph.D.
President and Chief Executive Officer

Exhibit 31.2

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

I, Steve E. Krognes, certify that:

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

Date: February 27, 2020

/s/ Steve E. Krognes

Steve E. Krognes
Chief Financial Officer and Treasurer

Exhibit 32.1

**CERTIFICATION OF CHIEF EXECUTIVE OFFICER
PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, (the “Exchange Act”) and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), I, Ryan J. Watts, Ph.D., President and Chief Executive Officer of Denali Therapeutics Inc. (the “Company”), hereby certify that:

1. The Company’s Annual Report on Form 10-K for the fiscal year ended December 31, 2019, to which this Certification is attached as Exhibit 32.1 (the “Periodic Report”), fully complies with the requirements of Section 13(a) or Section 15(d) of the Exchange Act; and

2. The information contained in the Periodic Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 27, 2020

By:	/s/ Ryan J. Watts
Name:	Ryan J. Watts, Ph.D.
Title:	President and Chief Executive Officer

Exhibit 32.2

**CERTIFICATION OF CHIEF FINANCIAL OFFICER
PURSUANT TO
18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002**

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended, (the "Exchange Act") and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), I, Steve E. Krognes, Chief Financial Officer and Treasurer of Denali Therapeutics Inc. (the "Company"), hereby certify that:

1. The Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2019, to which this Certification is attached as Exhibit 32.2 (the "Periodic Report"), fully complies with the requirements of Section 13(a) or Section 15(d) of the Exchange Act; and

2. The information contained in the Periodic Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: February 27, 2020

By:	/s/ Steve E. Krognes
Name:	Steve E. Krognes
Title:	Chief Financial Officer and Treasurer