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

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2018

OR

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

For the transition period from _____ to _____

Commission File Number: 001-38311

Denali Therapeutics Inc.

(Exact name of registrant as specified in its charter)

Delaware	**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)

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes x 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 x

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 x 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 x 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. x

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	x
Non-accelerated filer	☐	Smaller reporting company	☐
		Emerging growth company	x

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. x

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

The aggregate market value of the common stock held by non-affiliates of the registrant as of June 29, 2018 (the last business day of the registrant's most recently completed second fiscal quarter) was approximately $489.4 million, based on the closing price of the registrant's common stock, as reported by the NASDAQ Global Select Market on June 29, 2018 of $15.25 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 March 5, 2019 was 95,289,047 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 2018 fiscal year ended December 31, 2018.

Denali Therapeutics Inc.
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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, core programs and biomarkers;
- the extent to which any dosing limitations that we have been subject to and/or may be subject to in the future, may affect the success of our product candidates;
- the impact of preclinical findings on our ability to achieve exposures of our product candidates that allow us to explore a robust pharmacodynamic range of these candidates in humans;
- the expected potential benefits 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;
- our financial performance; and
- our expectations regarding the period during which we qualify as an emerging growth company under the JOBS Act.

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

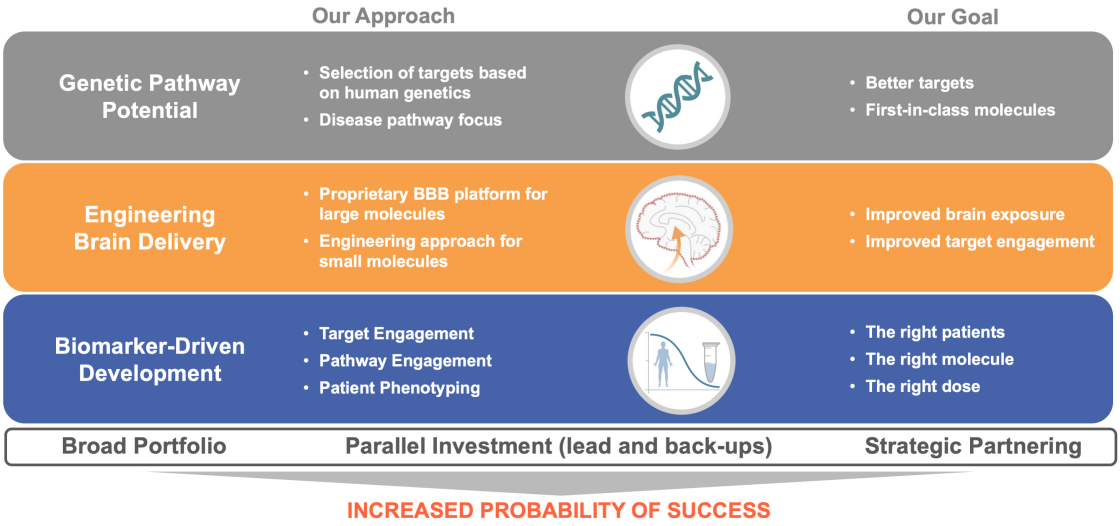
Our goal is to discover and develop therapeutics to defeat degeneration.

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

We believe the time is right to make a strong and ambitious effort to defeat neurodegeneration. We believe that we can succeed in a field that has seen limited success in the past, because of our team of experienced and passionately dedicated scientists and drug developers, our focused scientific strategy, and our proprietary blood-brain barrier ("BBB") platform delivery technology. 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 two programs in patient studies for Alzheimer's disease, Parkinson's disease, and ALS and two programs starting IND-enabling studies for Hunter Syndrome and Parkinson's disease.

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

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



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

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

To further increase the probability of success, 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.

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

We have development and commercialization rights to all of our programs, including the programs partnered with Takeda Pharmaceutical Company Limited ("Takeda"), as well as with Genzyme Corporation, a wholly owned subsidiary of Sanofi S.A. ("Sanofi") for CNS indications, where we share responsibility for clinical development and share commercialization rights in the US and China.

The following table summarizes key information about our programs:

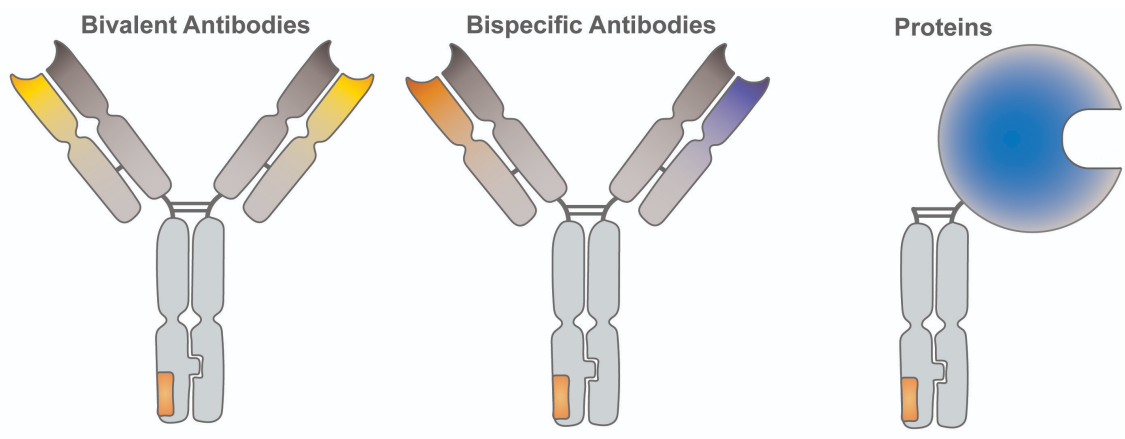
PROGRAM TARGET	DRUG CANDIDATE	DISEASE INDICATION	DRUG DEVELOPMENT	PARTNER
			Drug Discovery / IND-Enabling / Early Clinical / Late Clinical / Approved	
LYSOSOMAL FUNCTION PATHWAY				
LRRK2	DNL201 LEAD	Parkinson's	Early Clinical	
	DNL151	Parkinson's	Early Clinical	
Iduronate 2-sulfatase	DNL310	MPS II (Hunter Syndrome)	IND-Enabling	
Alpha-Synuclein	ATV:aSyn	Parkinson's, DLB, MSA	IND-Enabling	
Undisclosed	LF1	Neurodegeneration	Drug Discovery	Takeda
GLIAL BIOLOGY PATHWAY				
RIPK1 (CNS)	DNL747	Alzheimer's, ALS, MS	Early Clinical	Sanofi
TREM2	ATV:TREM2	Alzheimer's	Drug Discovery	Takeda
CELLULAR HOMEOSTASIS				
Tau	ATV:Tau	Alzheimer's	Drug Discovery	Takeda
Undisclosed	CH1	Neurodegeneration	Drug Discovery	
OTHER				
RIPK1 (Peripheral)	DNL758	RA, Psoriasis	IND-Enabling	Sanofi

Large Molecule (Transport Vehicle) Small Molecule

In addition to the programs listed above, Denali is also pursuing a number of SEED programs in Drug Discovery and IND-enabling stages of development

Delivering therapeutics across the BBB is critical to enabling effective treatments for CNS diseases, but this has been a major obstacle to successful drug development. Protein therapeutics, such as antibodies, have revolutionized the treatment of many diseases, but this class of medicines does not effectively cross the BBB and, therefore, currently has very limited therapeutic application to the treatment of CNS diseases. To address this limitation, we have developed proprietary drug delivery platform technologies, the most advanced of which is the TV platform. This technology enables the delivery of antibodies (Antibody Transport Vehicle or "ATV"), enzymes (Enzyme Transport Vehicle or “ETV") and other proteins (Protein Transport Vehicle or “PTV"). We have achieved proof of concept for the ATV and ETV platforms in mouse and nonhuman primate models. We are currently optimizing and broadening this platform technology.

Our ATV and ETV platforms are modular BBB delivery technologies for large molecule therapeutics, including antibodies, enzyme and other proteins.



Therapeutic candidates enabled by the TV platform are designed to engage specific BBB transport receptors, which are ubiquitously expressed in the brain capillaries and facilitate transport of proteins into the brain. Data from both mouse and nonhuman primate animal models across multiple studies designed to demonstrate proof of concept of the ATV and ETV platforms have demonstrated a robust and sustained pharmacodynamic (“PD”) effect in the brain after intravenous dosing of ATV-enabled antibodies and ETV-enabled recombinant enzymes, while standard antibodies and conventional recombinant enzymes had minimal PD effect. Antibodies engineered with our ATV technology have demonstrated an increase in brain exposure of approximately 20-fold, compared to control antibodies not enabled by this technology, which translates to a brain to plasma ratio of approximately 2%, compared to approximately 0.1% brain concentrations commonly observed for control antibodies not enabled by this technology. The improvement in brain exposure may enable therapeutically relevant concentrations of our ATV and ETV product candidates in the brain, making them potentially superior to traditional monoclonal antibodies, enzyme replacement therapies and other large molecule therapeutics.

We are currently developing several product candidates for multiple programs to advance into investigational new drug ("IND") enabling studies in preparation for human clinical trials. We plan to have multiple product candidates that utilize our TV platforms enter clinical development in 2019 and 2020, including molecules targeting alpha-synuclein ("aSyn"), iduronate 2-sulfatase ("IDS"), and triggering receptor expressed in myeloid cells 2 ("TREM2"); and Tau. In January 2018, we entered into an Option and Collaboration Agreement ("Takeda Collaboration Agreement") with Takeda pursuant to which we granted Takeda an option to develop and commercialize, jointly with us, three of our programs (ATV:TREM2 and ATV:BACE1/Tau and a third identified, but yet undisclosed discovery stage program) that are enabled by our TV blood-brain barrier delivery technology and intended for the treatment of neurodegenerative diseases. In February 2019, we amended the agreement with Takeda to replace the ATV:BACE1/Tau program with the ATV:Tau program, targeting only Tau. Based on progress with two of the three partnered programs, the criteria for certain defined milestones were met in the quarter ended December 31, 2018 and certain milestone payments received. If Takeda exercises its option for a particular target, we and Takeda will share equally the clinical development costs and the commercial profits for each collaboration program on a world-wide basis.

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

LRRK2 is a protein that regulates the function of the lysosome, an important cellular organelle involved in the physiological degradation of proteins. Increased LRRK2 activity is associated with perturbed lysosomal function, leading to reduced protein degradation and resulting in protein accumulation and cell death. Lysosomal dysfunction is a central pathology of Parkinson’s disease. Further, LRRK2 is genetically validated as a degenogene (a gene that causes or is a risk factor for neurodegenerative disease) as mutations in LRRK2 are one of the most commonly known genetic causes of Parkinson’s disease. Inhibiting LRRK2 with a brain-penetrant small molecule drug may improve lysosomal function and result in therapeutic benefit for patients with Parkinson’s disease. In a Phase 1 study in healthy volunteers, our lead LRRK2 product candidate, DNL201, met all objectives including CSF exposure levels and LRRK2 inhibition, as well as evidence of pathway engagement, at doses that were well tolerated. In December 2018, we initiated a Phase 1b clinical trial for DNL201 in Parkinson’s disease, including patients that carry a LRRK2 mutation and those without a LRRK2 mutation, i.e. sporadic Parkinson’s disease. In addition, we are conducting an ongoing Phase 1 healthy volunteer study with our back-up LRRK2 product candidate, DNL151. We intend to select one drug candidate for pivotal studies.

RIPK1 is a protein that regulates the function of microglia, which are the resident immune cells in the brain and genetically implicated in the pathology of neurodegenerative diseases. Increased RIPK1 kinase activity drives neuroinflammation and necroptotic cell death. Inhibition of RIPK1 has been shown to have beneficial effects in preclinical models of Alzheimer's disease, ALS and other diseases, including many systemic inflammatory diseases. In a Phase 1 study in healthy volunteers, our lead RIPK1 product candidate, DNL747, met all endpoints, including CSF exposure levels, RIPK1 inhibition, and pathway engagement, at doses that were well tolerated. In December 2018, we initiated a Phase 1b clinical trial for DNL747 in ALS and in February 2019 we initiated a Phase 1b clinical trial for DNL747 in Alzheimer's disease. We have additional RIPK1 back-up candidates, including one that has completed IND-enabling studies. In October 2018, we entered into a Collaboration and License Agreement with Sanofi ("Sanofi Collaboration Agreement"). Denali and Sanofi plan to jointly develop and commercialize 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.

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, Sanofi, Genentech, 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.

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, 5.7 million people suffer from Alzheimer's disease, as many as one million people suffer from Parkinson's disease, and more than 20,000 patients suffer from ALS, according to estimates from the Alzheimer's Association, the Parkinson's Disease Foundation, and the ALS Association, respectively.

The cost to society from neurodegenerative disease is massive. The direct costs of caring for individuals with Alzheimer's disease and other dementias in the United States were an estimated $277 billion in 2018, and are projected to increase to $1.1 trillion by 2050, according to the Alzheimer's Association. In the United States, the total cost of care to patients suffering from Alzheimer's disease and other dementias far exceeds that of many other diseases, including cancer.

Our Scientific Strategy

We strictly follow our scientific strategy, which consists of three principles below, and we believe that this will increase our probability of success and accelerate development timelines:

- Genetic pathway potential: selection of targets with a genetic link to disease;

- Engineering brain delivery: specifically designing therapeutics to cross the blood-brain barrier; and
- Biomarker-driven clinical development: Selecting the right patients, selecting the right dose, and monitoring effects of the drug in early clinical studies.

Genetic Pathway Potential

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

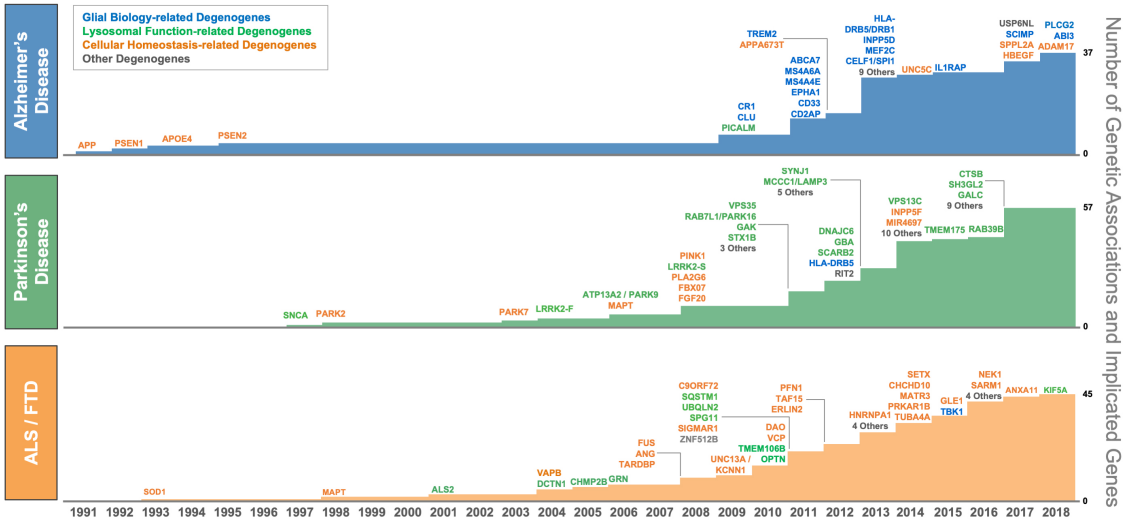
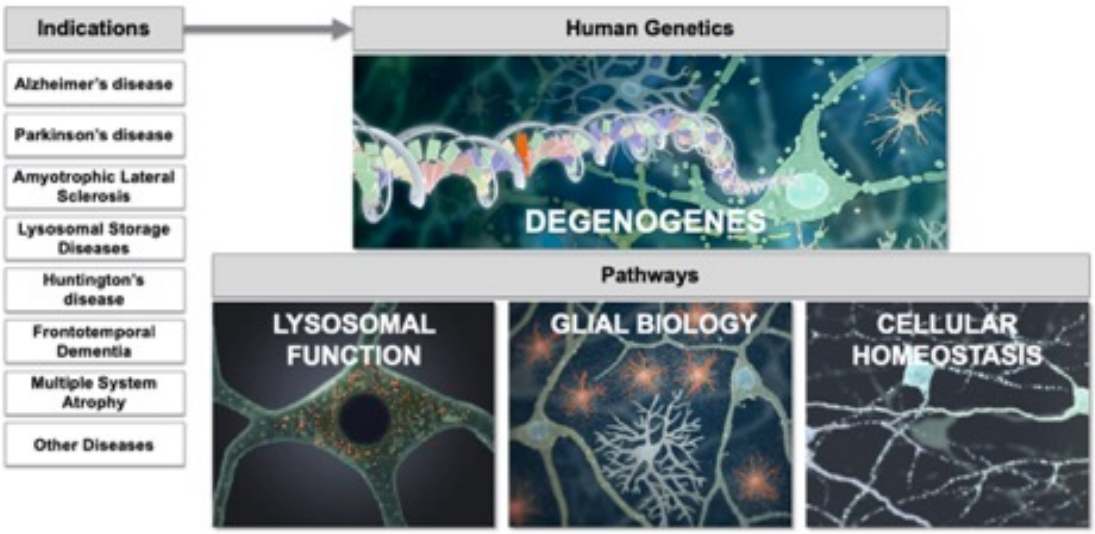


Figure 1: The number of associated genetic mutations linked to Alzheimer's disease, Parkinson's disease and ALS from 1991 to 2018. For genome-wide association studies, disease genes were selected based on genome-wide significance ($p<5\times10-8$). Rare disease-causing and/or high penetrance mutations were included based on a p value of 1x10^-7 and replication in an independent cohort.

Human Genetics: Degenogenes

Prior to 2007, only a limited number of genetic mutations linked to Alzheimer's disease, Parkinson's disease and ALS had been identified. Since 2007, the number of genetic associations discovered in neurodegenerative diseases has grown rapidly, with more than 130 genes associated with these three neurodegenerative diseases collectively. These degenogenes directly point to important disease pathways that are disrupted in neurodegeneration, and are our scientific foundation for identifying and pursuing promising targets for drug development. We have chosen to initially focus on three such pathways: lysosomal function, glial biology and cellular homeostasis.



Disease Pathways

Lysosomal Function

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

Glial Biology

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

Cellular Homeostasis

Many degenogenes directly alter the homeostatic balance of brain cells. Specifically, defects in protein, ribonucleic acid ("RNA") or metabolic homeostasis lead to the death of neurons and dysfunction of the nervous system. This includes spreading of protein aggregates resulting in a proteinopathy, a characteristic finding in Alzheimer's and Parkinson's diseases that results from disorders of protein synthesis, trafficking, folding, processing or degradation in cells. This also includes aggregation of RNA binding proteins disrupting cellular stress response in Alzheimer's disease and ALS. The clearance of macromolecules in the brain is particularly susceptible to imbalances that result in aggregation and degeneration in nerve cells. For example, Alzheimer's disease pathology is characterized by the presence of amyloid plaques, which are accumulations of complex amyloid proteins deposited in tissues and neurofibrillary tangles, which are aggregates of hyperphosphorylated Tau protein that are a marker of Alzheimer's disease and other diseases known as tauopathies. We target this pathology with our ATV:Tau program and believe therapies that correct defects in cellular homeostasis have the potential to halt or delay neurodegenerative disease progression.

Engineering Brain Delivery

The Blood-Brain Barrier Challenge

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

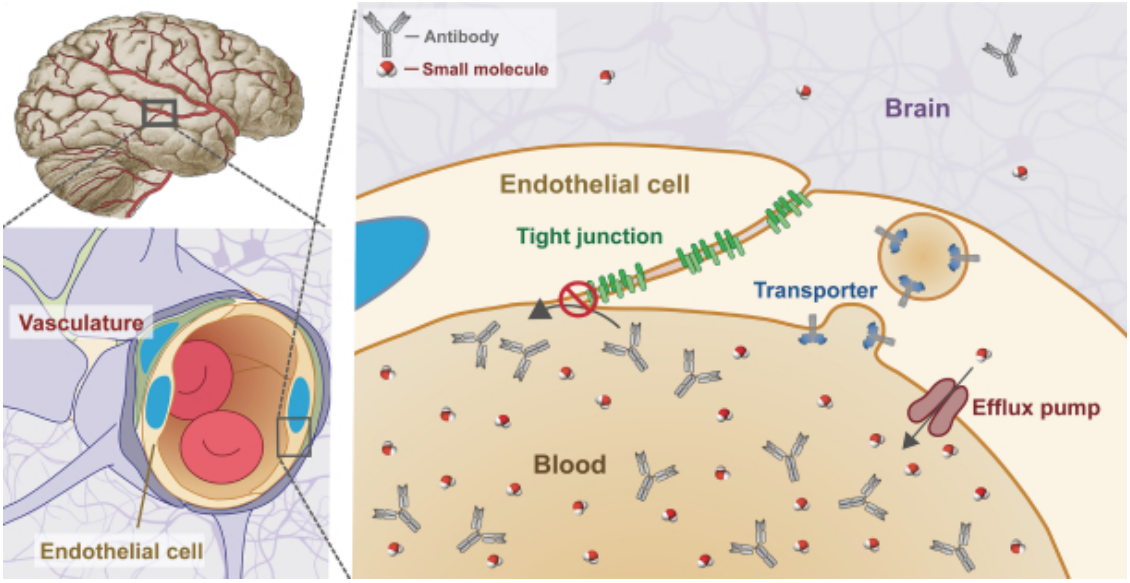


Figure 2: Schematic of the BBB. The specialized vessels of the brain represent a significant barrier for both small and large molecule therapeutics. Tight junctions between endothelial cells prevent the diffusion of large molecules while most small molecules are kept out of the brain by efflux pumps.

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

Engineering Large Molecule Brain Delivery

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

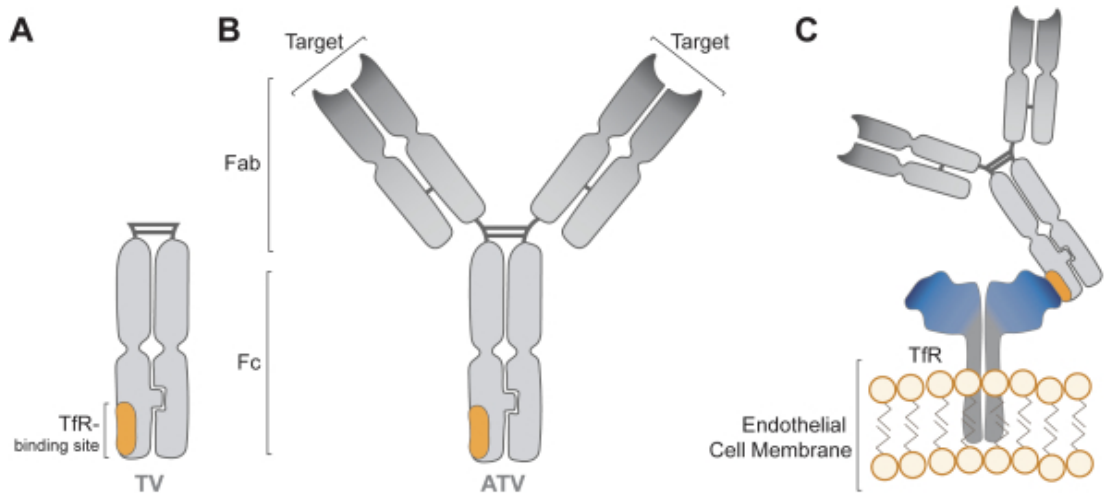


Figure 3: Schematic of the BBB large molecule Transport Vehicle (TV) technology. The TV platform technology contains BBB receptor (TfR) binding in the Fc domain (A). The TV can be fused to Fab arms constituting the Antibody Transport Vehicle (ATV) technology (B). ATVs bind to TfR, enabling TfR-mediated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

Antibody Transport Vehicle

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

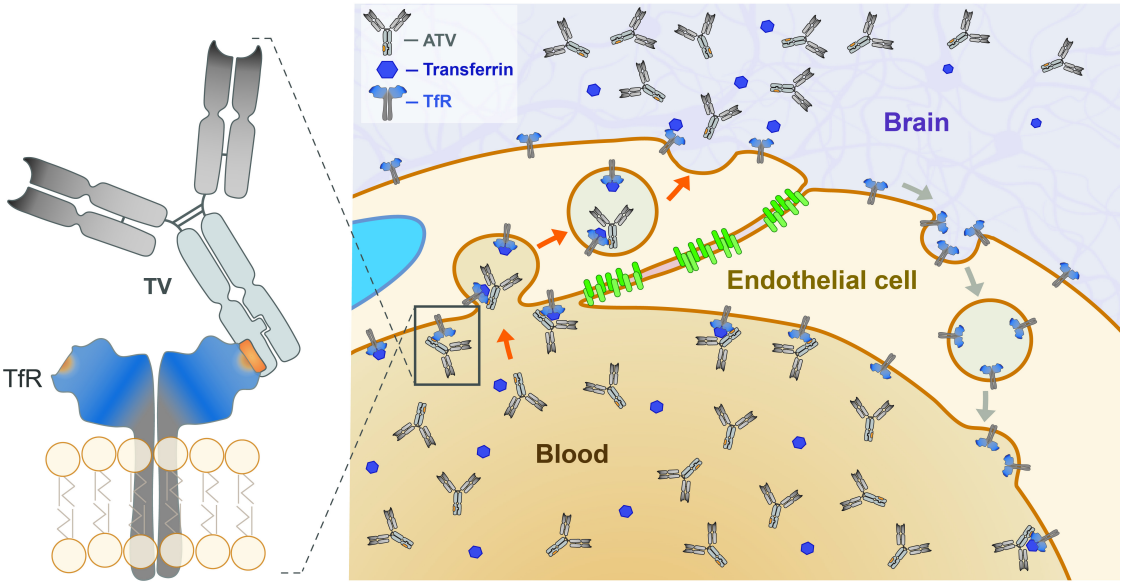


Figure 4: Schematic of receptor-mediated transport of ATV at the BBB. ATV molecules engage TfR on the blood vessel wall in the brain. Once bound, ATV is brought into vesicles that are transcytosed across the endothelial cell and released into the brain, thus substantially increasing antibody concentrations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

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

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

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

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

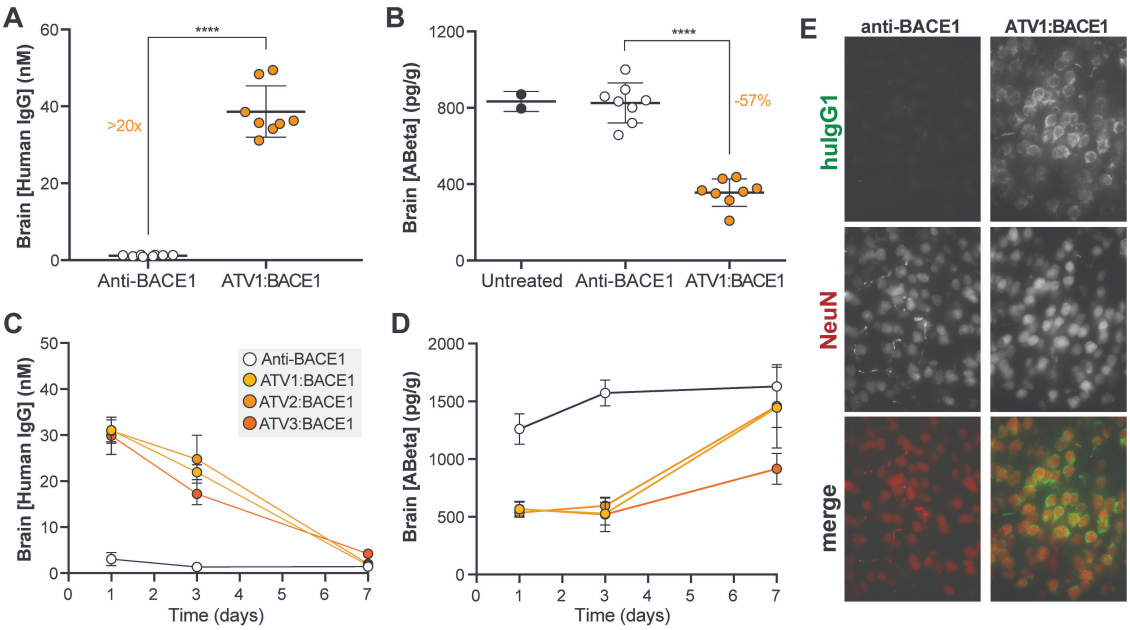


Figure 5: ATV therapeutics achieve robust brain uptake and PD activity in human TfR knock-in mice. Mice were injected with 50 mg/kg of anti-BACE1 or ATV1:BACE1. After 24 hours of circulation, brain antibody concentrations were compared between anti-BACE1 (1.2nM) and ATV1:BACE1 (38.6nM) (A). A significant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

To further validate the ATV platform, we completed an i*n vivo* study in nonhuman primates with an ATV designed to bind to cynomolgus monkey TfR (ATV4:BACE1). Data from this 28-day study demonstrated a robust and sustained brain PD response as measured from fluid taken from brains of living monkeys (Figure 6). When measuring drug activity in blood (plasma) versus brain (CSF), both anti-BACE1 and ATV4:BACE1 show robust activity in the blood, however only the ATV-enabled antibody (ATV4:BACE1) demonstrated robust and sustained PD activity in the nonhuman primate brain. We believe these *in vivo* proof of concept data in nonhuman primates provide support for the translatability of the ATV platform for human studies.

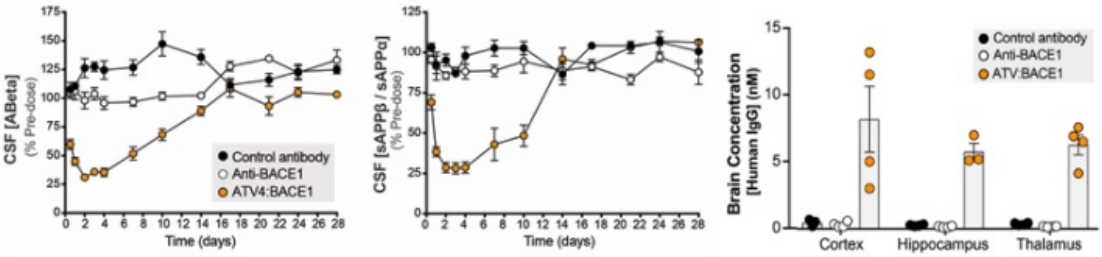


Figure 6: ATV therapeutics achieve CNS PD activity in nonhuman primates. Cynomolgus monkeys were systemically injected with 30 mg/kg of control antibody, anti-BACE1, or ATV4:BACE1. In plasma, anti-BACE1 and ATV4:BACE1 equally reduce Abeta levels (A). In CSF, a robust and sustained reduction in CSF Abeta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

Enzyme Transport Vehicle

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

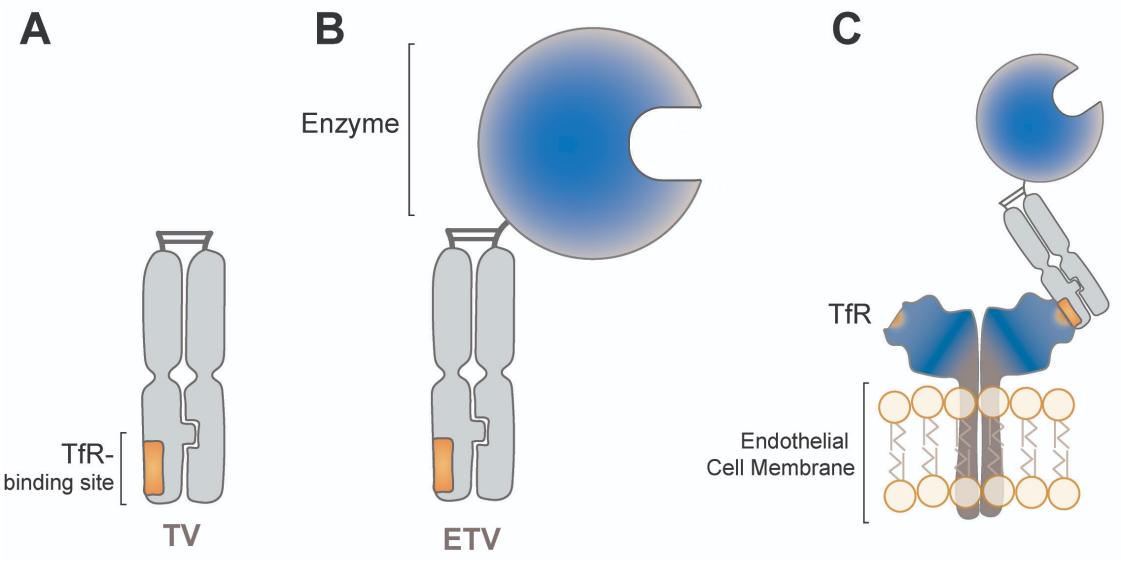


Figure 7: Engineering brain delivery using the ETV platform. The ETV platform technology contains BBB receptor (TfR) binding in the Fc domain (A) fused to an enzyme (B) to enable transport of enzymes into the brain through TfR-mediated transcytosis (C).

Platform Technology Development and Applications

We are advancing our ATV and ETV platforms through further preclinical studies in mice and nonhuman primates. We are currently undertaking or plan to commence additional IND-enabling studies for multiple preclinical product candidates in 2019, including DNL310 (ETV:IDS) in Hunter Syndrome and ATV:aSyn in Parkinson's disease. We plan to file an IND or CTA for our first platform-enabled program, DNL310 (ETV:IDS) in late 2019. We are also combining our proprietary human TfR knock-in-mice model with disease-specific animal models in order to more precisely assess the potential of our platform-enabled therapeutic candidates in relevant disease models. We expect that this will give us the ability to perform pharmacokinetic/pharmacodynamic ("PK/PD"), and efficacy studies and to quantitatively demonstrate the advantages of antibodies and proteins delivered using our platform technologies. To enable the development of our platform technologies, we have entered into a strategic licensing and collaboration agreement with F-star. For more information regarding our collaborations, see "Business - Licenses and Collaborations."

Engineering Small Molecule Brain Delivery

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

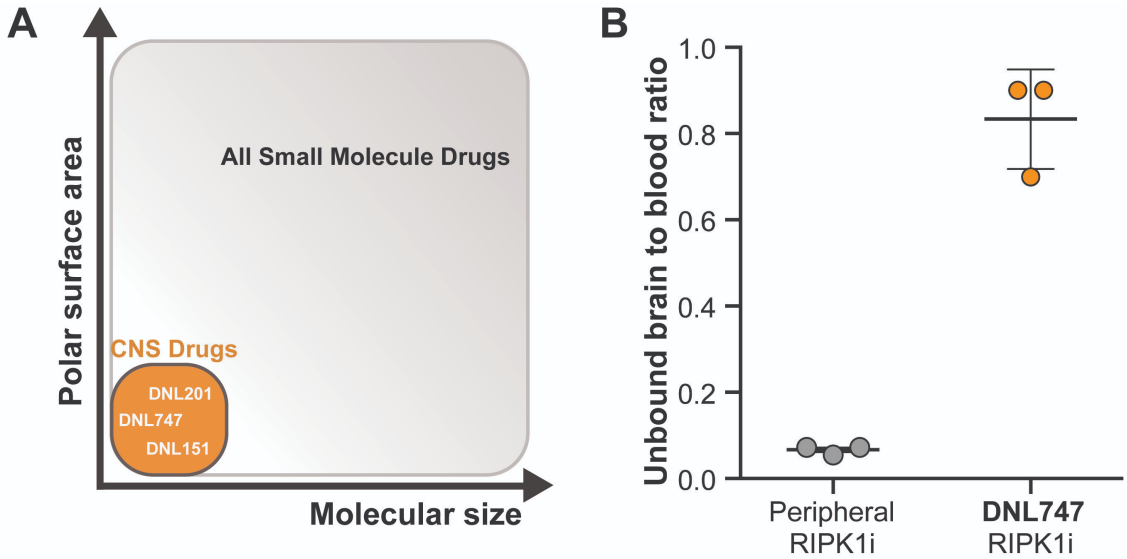


Figure 8: Generation of brain penetrant small molecules. The molecular properties compatible with CNS drugs are significantly more restricted than those generally used to design small molecule drugs, including tight restrictions on molecular weight and total polar surface area (A). This figure is not to scale. An example of how molecular properties influence brain penetration is shown in (B), where our lead RIPK1 inhibitor DNL747 displays a brain to blood ratio of ~0.8 while a benchmark periphery-restricted RIPK1 inhibitor displays a ratio of ~0.05.

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

Biomarker-Driven Clinical Development

We define biomarker goals at every phase of development, including prior to the filing of an IND. We focus on three biomarker-driven development principles: target engagement, pathway engagement and patient phenotyping.

Biomarker discovery begins in early preclinical stages for each project. This early preclinical work provides a strong foundation for clinical biomarker work. In-depth investigations into target biology suggest biomarkers of target and pathway engagement that can be explored preclinically in cellular and animal models. Assessment of biomarkers in preclinical animal models enables elucidation of the relationship of target engagement in an accessible peripheral tissue (e.g. blood) and target engagement in the brain (e.g. brain and CSF).

The preclinical biomarkers for target and pathway engagement can be tested in Phase 1 human healthy volunteer or patient studies to confirm translatability of the findings and assess CNS target engagement and its relationship to drug exposure.

The disease relevance of these markers can also be evaluated in biosamples taken from the relevant patient population and then evaluated in patient studies to generate data linking target and pathway engagement to relevant effects on abnormal disease biology. This approach is intended to increase the likelihood of success in Phase 2 and Phase 3 clinical endpoint studies by enabling early dose finding in our clinical programs and streamlining overall clinical development. By utilizing biomarkers and genetic information, we can also better select the best patient population for our clinical trials and product candidates.

Our Portfolio

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 continually evaluate new programs through our in-house discovery and partnering efforts and employ a rigorous process of prioritization and resource allocation to maintain an optimal balance between aggressively advancing existing programs, discontinuing programs which fail to meet key success criteria, and initiating new programs.

We discuss six of our programs in further detail below.

LRRK2 Inhibitor Program

The two most advanced LRRK2 product candidates are potent, selective and brain-penetrant small molecule inhibitors under investigation for treatment of Parkinson’s disease. DNL201 is in a Phase 1b clinical trial enrolling Parkinson’s disease patients both with and without a genetic LRRK2 mutation. DNL151 is in a Phase 1 clinical trial in healthy volunteers.

Therapeutic Rationale

Lysosomal dysfunction is a central pathology of Parkinson’s disease. Genetic mutations in several proteins associated with Parkinson’s disease, including LRRK2, GBA and aSyn, disrupt normal lysosomal function and contribute to neurodegeneration and the formation of Lewy bodies, which are intracellular aggregates containing aSyn proteins (Figure 9). LRRK2 regulates lysosomal function by phosphorylating Rab proteins, which control intracellular lysosomal trafficking (Figure 10). 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.

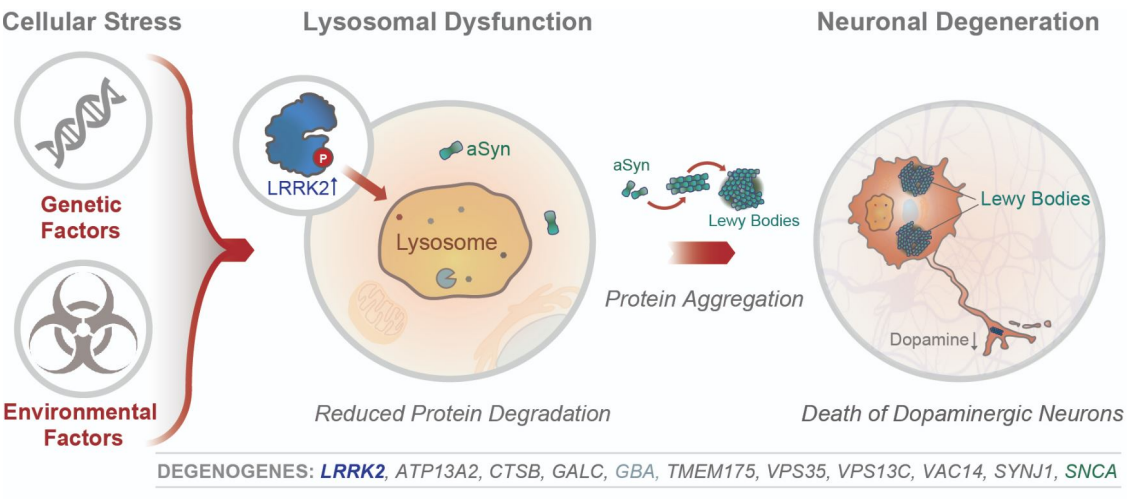


Figure 9: Lysosomal dysfunction is a central pathology in Parkinson's disease and leads to protein aggregation of aSyn and Lewy bodies and the death of dopaminergic neurons. LRRK2 acts in healthy cells to maintain normal lysosomal function. Excessive LRRK2 activation or expression reduces lysosomal function and contributes to the progression of Parkinson's disease. Lysosomal dysfunction in Parkinson's disease can also be caused by other genetic factors as well as environmental factors. LRRK2 inhibition can restore normal lysosomal function and reduce toxicity in Parkinson's disease models.

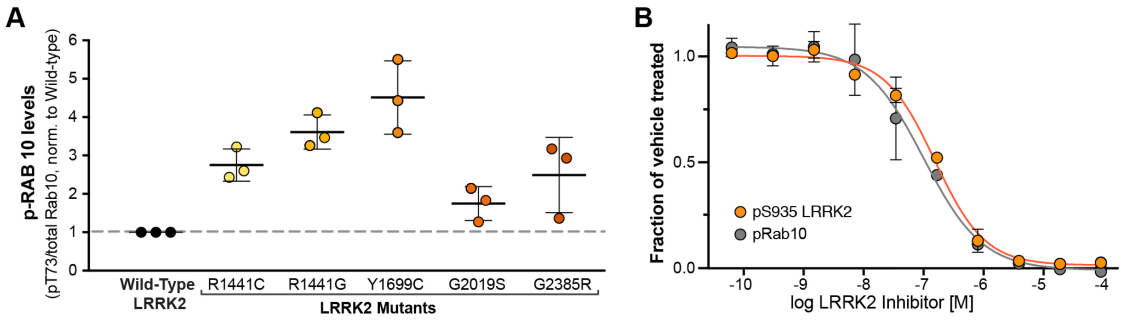


Figure 10. Phosphorylated Rabs are a novel marker of LRRK2 activity. Multiple distinct LRRK2 mutations result in elevated phosphorylation of the downstream marker Rab10 (A), while inhibition of LRRK2 results in a dose-dependent inhibition of Rab10 phosphorylation that is comparable to the inhibition of LRRK2 phosphorylation on Serine 935 (B).

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

Pharmacological Properties and Brain Exposure

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

Both DNL201 and DNL151 displayed comparable potency of LRRK2 inhibition in blood cells taken from LRRK2 mutation carriers and non-carriers, with a small apparent increase in potency in cells from G2019S mutation carriers (Figure 11).

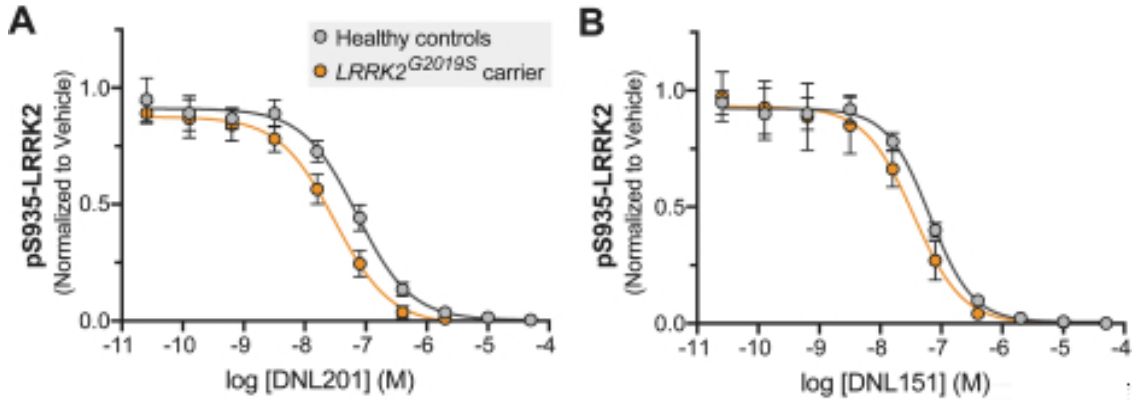


Figure 11. Treatment of peripheral blood mononuclear cells (PBMCs) derived from LRRK2 mutation carriers and healthy control non-carriers with our LRRK2 inhibitors. Both DNL201 (A) and DNL151 (B) demonstrated a small increase in potency in PBMCs from G2019S mutation carriers.

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 BMP di22:6 in urine and CSF of subjects treated with LRRK2 inhibitors. BMP di22:6 is a lysosomal lipid biomarker that indicates changes in lysosome function associated with LRRK2 inhibition.

Results of phase 1 clinical study in healthy volunteers

The DNL201 Phase 1 clinical trial in healthy volunteers 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.

Safety

DNL201 was generally well tolerated with no serious adverse events at doses that achieved high levels of CSF exposure and effects on biomarkers of lysosomal function. All treatment emergent adverse events (“TEAEs”) were mild or moderate in severity. In the single ascending dose (“SAD”) study, single doses from 10 mg to 225 mg were evaluated, and in the multiple ascending dose (“MAD”) study, multiple doses from 40 mg once daily and 25 mg to 150/100 mg twice daily were evaluated. The most common TEAs in the MAD study were headache, dizziness, and nausea.

At the highest doses studied, small C_{max} related mean increases in pulse rate and mild decreases in blood pressure were observed, but were generally well tolerated. There were no clinically meaningful changes on ECGs, neurological exams, safety laboratories, renal parameters or pulmonary function tests. Overall, the maximum tolerated multiple dose was 100 mg BID, and in the healthy elderly cohort a dose of 80 mg BID was studied and was generally well tolerated. These data supported the advancement of DNL201 into a Phase1b study in Parkinson patients with and without a LRRK2 mutation.

Pharmacokinetics

The PK profile of DNL201 was well behaved and CSF/unbound plasma ratios reflected extensive distribution of DNL201 into the CNS.

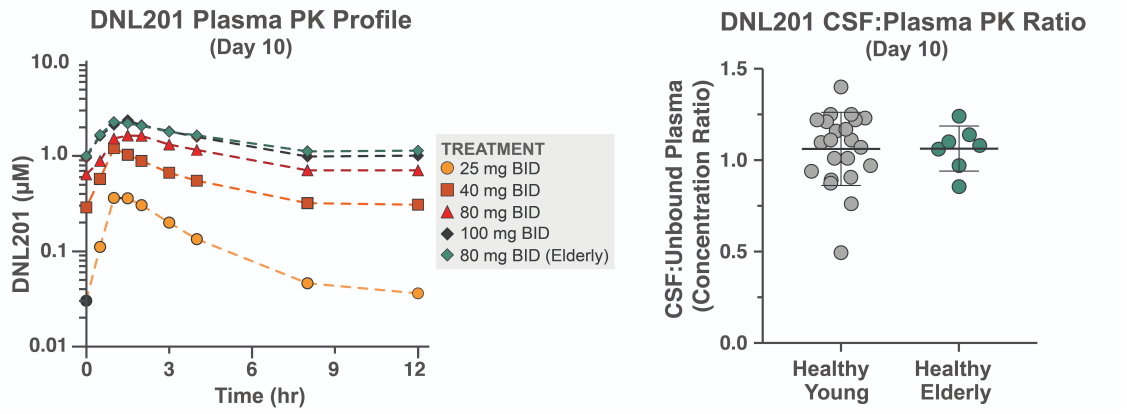


Figure 12: DNL201 concentration-time profiles and CSF exposure in healthy young and elderly subjects following administration of multiple oral doses of DNL201.

Target and Pathway Engagement

Dose- and exposure-dependent reductions of both pS935 LRRK2 and pRab10 were observed following administration of well-tolerated doses of DNL201 in healthy volunteers, including healthy elderly subjects.

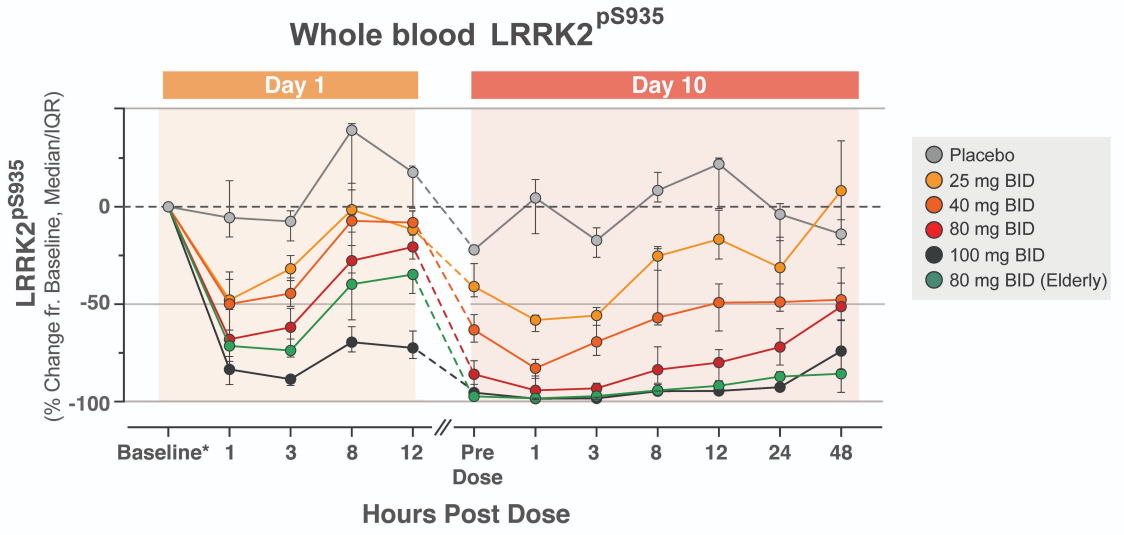


Figure 13: DNL201 dose-dependent inhibition of LRRK2 in healthy subjects as measured by phosphorylation of LRRK2 on Serine 935 in blood samples collected on Day 1 and Day 10 of dosing. 50% inhibition at trough (Day 10 12 hours post-dose) was achieved in the 40 mg BID group, demonstrating that doses greater than or equal to 40 mg BID are therapeutically relevant.

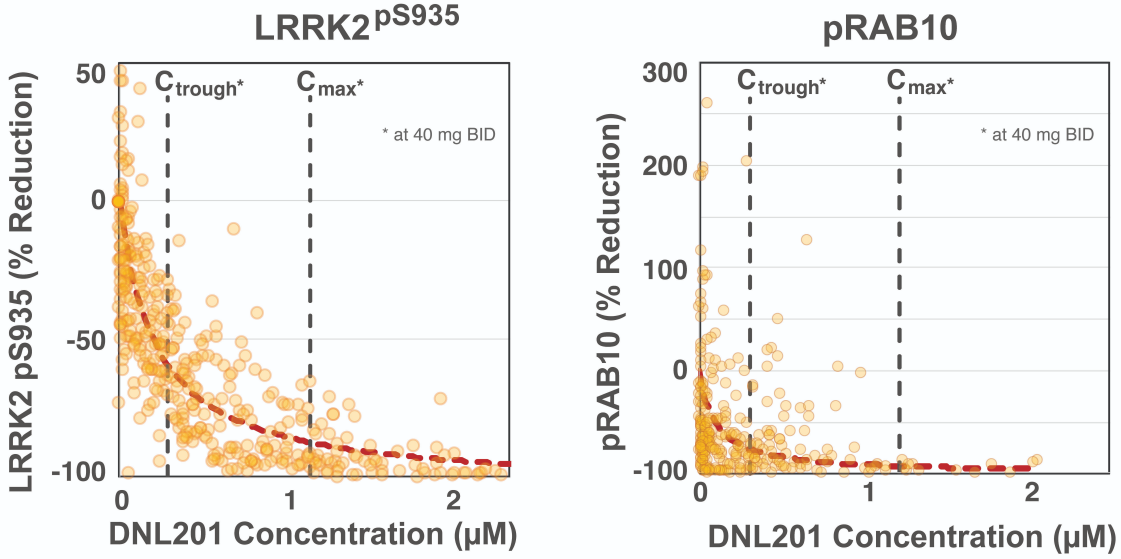


Figure 14: DNL201 exposure-response in healthy subjects, as measured by phosphorylation of LRRK2 on Serine 935 and phosphorylation of Rab10. Vertical dashed lines show >50% inhibition at trough (Day 10 12 hours post-dose) and >80% inhibition at Cmax (Day 10 3 hours post-dose) in the 40 mg BID group. Greater inhibition at trough and Cmax was achieved in higher dosed cohorts.

Future Development Plan

In December 2018, we initiated a Phase 1b study of DNL201 Parkinson's disease patients with and without LRRK2 mutations. The primary objectives of this trial are to evaluate safety, PK and PD of DNL201 in LRRK2 patients to identify the optimal dose(s) to study in future Phase 2 and Phase 3 clinical trials, and confirm relevant biomarkers. In addition to ongoing clinical studies, we have engaged Centogene to conduct a targeted global recruitment campaign focused on the early identification and characterization of LRRK2 PD patients and sequence the LRRK2 gene in these patients, to enroll in future clinical studies.

The Phase 1 clinical trial in healthy volunteers for DNL151 is ongoing and we expect to complete this study in 2019.

RIPK1 Inhibitor Program

The most advanced product candidate in our RIPK1 inhibitor program, DNL747, is a potent, selective and brain-penetrant small molecule RIPK1 inhibitor. 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"). We commenced DNL747 Phase 1b clinical trial in December 2018 for ALS and in February 2019 for Alzheimer's disease.

Therapeutic Rationale

Aberrant glial biology characterized by neuro-immune dysfunction is a cardinal feature of the pathology of many chronic neurodegenerative diseases including Alzheimer's disease and ALS. Genome wide association studies ("GWAS") identified that a large proportion of genetic risk factors for late-onset Alzheimer's disease are expressed almost exclusively by microglia, the resident immune cells of the brain, thus implicating microglia as an important effector of neurodegeneration. ALS-causing mutations in optineurin ("OPTN") result in increased RIPK1 activity in microglia, while two additional ALS-risk genes, Tank Binding Kinase ("TBK") and TNFAIP3-interacting protein 1 ("TNIP1"), regulate RIPK1 signaling in cell-based experiments and in preclinical animal models.

Stimulation of RIPK1 signaling in cultured microglia produces cytokines and other pro-inflammatory factors, including CCL2 ("MCP-1"), IL-1b, and IL-6, while treatment with RIPK1 inhibitors attenuates induction of these factors. Production of these pro-inflammatory cytokines by activated microglia can exacerbate tissue damage and neuronal death. An increase in RIPK1 has been observed both in the brains of animal models of chronic neurodegeneration and patients with Alzheimer's disease that is correlated with microglial cell activation, suggesting RIPK1 activation is increased in disease.

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

Biomarker-Driven Development

Target engagement has been characterized using a marker of RIPK1 activity, phosphorylation 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 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.

Safety

DNL747 was well tolerated to the highest doses tested with no serious adverse events at doses that achieved high levels of brain exposure and robust target engagement as measured by pS166 activity. Across both the SAD and MAD portions of the study there were 42 healthy subjects who received at least one dose of active DNL747, with no serious adverse events and no discontinuations due to study drug exposure. The majority of TEAEs were mild (92%) with the rest of moderate severity.

Pharmacokinetics

The PK profile of DNL747 was well behaved and CSF/unbound plasma ratios reflected extensive distribution of DNL747 into the CNS.

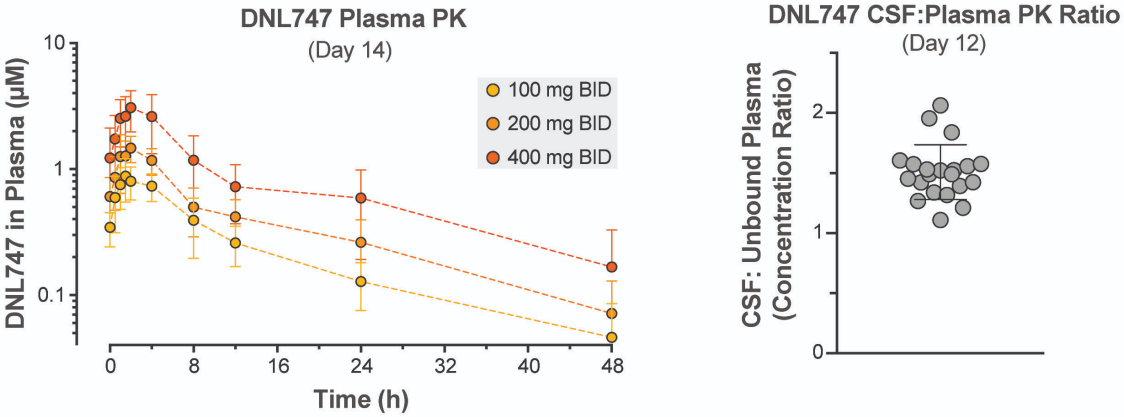


Figure 15: Left: Mean pharmacokinetic profiles of DNL747 at steady-state (Day 14), following oral 100, 200, or 400 mg BID doses to healthy volunteers. Right: CSF:plasma ratio of DNL747 concentrations at steady-state (Day 12), 4 hours post-dose, all dose groups combined. No effects of dose were observed.

Target and Pathway Engagement

A robust, dose-dependent reduction of RIPK1 at pS166 was observed following administration of DNL747 in healthy volunteers at all three doses.

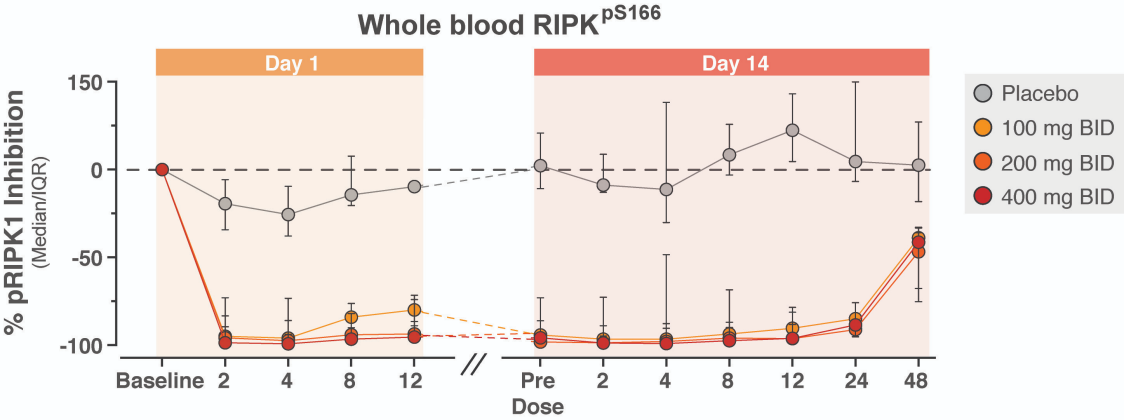


Figure 16: DNL747 dose-dependent inhibition of RIPK1 in healthy subjects as measured by RIPK1 Serine166 phosphorylation change in PBMCs in the multiple-ascending dose cohorts. Nearly 90% inhibition up to 12hrs is achieved with all three doses at the steady state of the dosing period.

Future Development Plan

In partnership with Sanofi, we commenced DNL747 Phase 1b clinical trial in December 2018 for ALS and in February 2019 for Alzheimer's disease. These are randomized, double blind, placebo controlled, cross-over designed studies. The primary objectives of these patient studies are to evaluate safety, PK and PD of DNL747 in Alzheimer's disease and ALS patients, to confirm evidence of target engagement in patients and confirm relevant biomarkers.

We are working with Sanofi to define the future clinical development plans for our RIPK1 inhibitor molecules in ALS, MS and Alzheimer's disease.

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 candidate for which IND-enabling studies have been completed. Sanofi will lead clinical development activities with DNL758 for all systemic inflammatory diseases. The clinical trials are expected to begin in 2019.

ETV:IDS Enzyme Replacement Therapy Program

We are developing ETV:IDS as a treatment for the lysosomal storage disorder MPS II. MPS II, also known as Hunter Syndrome, is an X-linked recessive genetic lysosomal storage disease caused by a single gene defect leading to a deficiency in the enzyme IDS. IDS is essential for the breakdown of the glycosaminoglycans ("GAGs"), heparan and dermatan sulfate, and its deficiency results in a toxic accumulation of GAGs and perturbed lysosomal function. Approximately two-thirds of MPS II patients suffer from the neuropathic form of the disease, which is characterized by intellectual disability and a progressive cognitive decline that emerges between three and five years of age. MPS II is currently treated with intravenous infusions of recombinant IDS protein. These treatments do not efficiently distribute to the brain and, therefore, cannot address the neurological manifestations of the disease. There is a demonstrated need for therapies that effectively cross the BBB so as to treat both neurological and peripheral manifestations of MPS II and other LSDs.

Using our TV technology, we have engineered therapeutic fusion proteins that effectively deliver IDS across the BBB into brain tissue in addition to distribution in the rest of the body. Our lead ETV:IDS candidate, DNL310, is currently in IND-enabling studies, and we plan to file an IND or CTA in late 2019.

We have achieved *in vivo* proof of concept for the ETV:IDS program in a mouse model of MPS II disease. ETV:IDS robustly lowered GAGs in the liver and spleen at levels comparable to idursulfase, a recombinant IDS protein and currently the standard of care for Hunter Syndrome. Importantly, we demonstrated that ETV:IDS was also highly effective in lowering GAGs in the brain, which was not achieved with conventional recombinant IDS as it does not cross through the BBB. The robust GAG reduction observed in brain translated to correction of downstream disease-relevant pathology as treatment with ETV:IDS resulted in a complete correction of lysosomal lipid accumulation and reduction in levels of TREM2, a marker of microglia activity, in the brain.

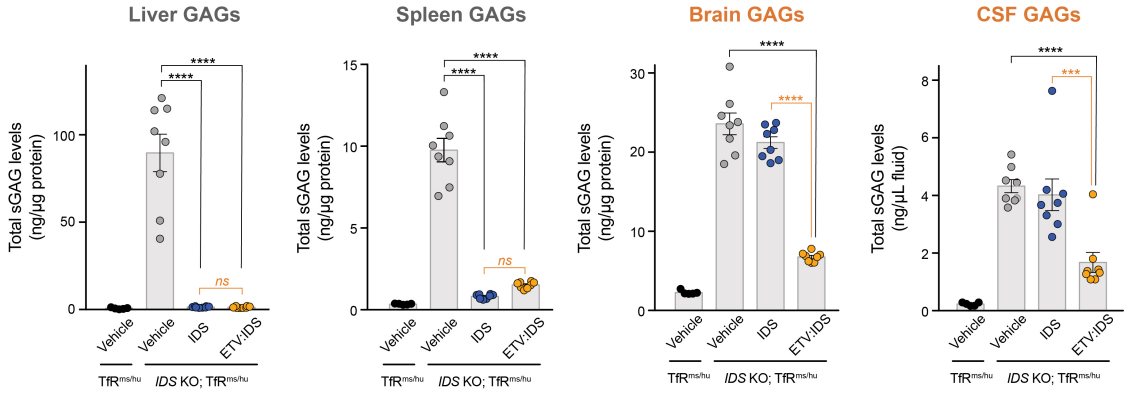


Figure 17: ETV:IDS reduces GAGs in the periphery of IDS KO; TfRmu/hu KI mice at the same level as conventional recombinant IDS. ETV:IDS has a superior effect in the brain and CSF while conventional recombinant IDS does not reduce GAGs in the brain.

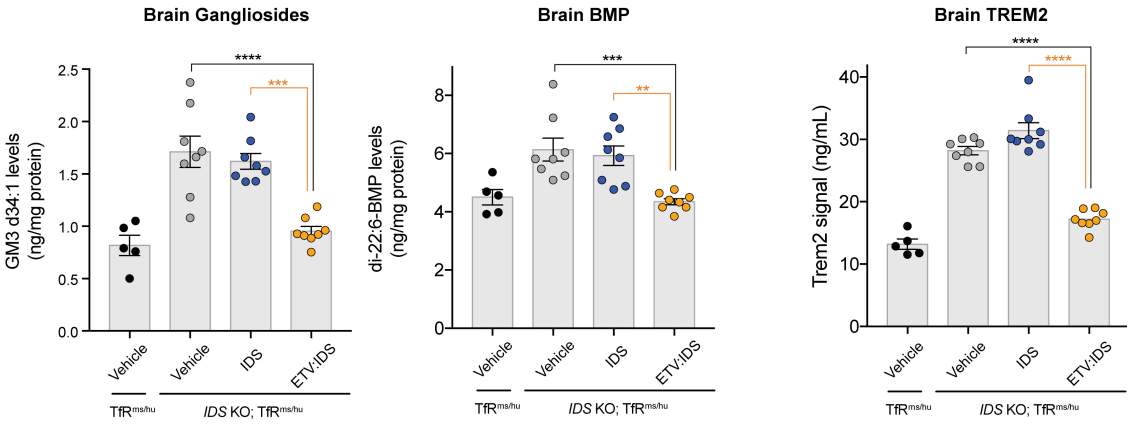


Figure 18: ETV:IDS corrects downstream pathology including lysosomal lipid storage and microglial activation, while conventional recombinant IDS does not have an effect of downstream pathology.

ATV:aSyn Program

ATV:aSyn is a therapeutic candidate targeting alpha Synuclein, a protein that pathologically accumulates, aggregates and spreads throughout the brain in Parkinson's disease. Lysosomal dysfunction in neurons can contribute to aSyn aggregation, which results in the formation of Lewy bodies, which are one of the defining neuropathological characteristic of Parkinson's disease, and ultimately cell death. Further, aSyn is a degenogene, as mutations in this gene lead to an increased risk for Parkinson's disease.

Our ATV:aSyn candidates are currently in preclinical development, and we expect to file an IND or CTA in 2020. Following proof of concept in Parkinson's disease, we may also explore clinical development for patients with other synucleinopathies, such as dementia with Lewy bodies and multiple system atrophy.

ATV:TREM2 Program

ATV:TREM2 is a therapeutic candidate designed to rescue microglial function in Alzheimer's disease through modulating the activity of TREM2, a degenogene. A major component of Alzheimer's disease pathology is the presence of neuro-immune dysfunction. Microglia, the resident immune cells of the brain, show signs of activation and release of toxic cytokines in patients with Alzheimer's disease. In 2013, a rare variant of TREM2 was found to be associated with a three-fold higher risk of Alzheimer's disease onset, which strongly implicates TREM2 as a functional contributor to disease progression.

We have developed high affinity antibodies for TREM2 and are currently characterizing antibodies in order to select a lead to couple with our proprietary ATV platform. We plan to file an IND or CTA for this program in 2021.

As described in more detail in "Business - Licenses and Collaborations" below, Takeda has the right to opt in to our ATV:TREM2 program.

ATV:Tau Program

ATV:Tau is a therapeutic targeting the spreading of Tau, a protein that when misfolded, forms neurofibrillary tangles. This pathology is a consequence of protein aggregation, a form of disrupted cellular homeostasis, eventually leading to neuronal degeneration. Tau is believed to regulate microtubule stability in neurons, but it can also aggregate to form neurofibrillary tangles present in many neurodegenerative diseases, including Alzheimer's disease.

We have developed high affinity antibodies for Tau and are currently optimizing the lead molecule on our proprietary ATV platform. We believe our ATV:Tau program will target a primary hallmark pathology of Alzheimer's disease with improved target engagement compared to competitors based on unique epitope and enhanced brain penetration. We plan to file an IND or CTA in 2021.

The ATV:Tau program replaces the ATV:BACE1/Tau program, which was discontinued based on emerging clinical data demonstrating that small molecule inhibitors of BACE1 may worsen cognition. As described in more detail in "Business - Licenses and Collaborations" below, Takeda has the right to opt in to our ATV:Tau program.

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 program, our ATV:TREM2 program, and a third identified, but yet undisclosed discovery stage program. 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 ATV:BACE1/Tau with ATV:Tau.

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 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 $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, Takeda will be obligated to pay us up to an aggregate of $707.5 million upon achievement of certain clinical and regulatory milestone events if Takeda exercises its option for all three collaboration programs. Further, Takeda will 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

On October 29, 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 for which IND-enabling studies have been completed.

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. 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 $600.0 million in clinical and regulatory milestone payments for CNS Products and $495.0 million in clinical, regulatory and commercial milestone payments for Peripheral Products.

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.

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 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 are conducting and will complete, 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 Phase 3 and later stage development trials for CNS Products, with Sanofi funding 70% of such costs and Denali funding 30% of such costs. 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 currently-planned Phase 1 trials 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 with F-star Gamma Limited, F-star Biotechnologische Forschungs-und Entwicklungsges m.b.H and F-star Biotechnology Limited (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.

On May 30, 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 has become 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 in the aggregate, of $18.0 million, less the net liabilities of F-star Gamma, which is 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. The amount of the contingent payments varies based on whether F-star delivers an Fcab (constant Fc-domains with antigen-binding activity) that meets pre-defined criteria and whether the Fcab has been identified solely by us or solely by F-star or jointly by us and F-star.

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 each agreed development plan, for up to 24 months. These research costs for the agreed TfR development plan were up to $2.1 million.

Genentech Exclusive License Agreement

In June 2016, we entered into an exclusive license agreement with Genentech. The agreement gives us access to Genentech's LRRK2 small molecule program. 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. 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 and success to have a reliable, high-quality preclinical and clinical drug supply. As we mature as a company and approach commercial stage operations, securing reliable high-quality commercial drug supply will be critical.

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

We rely on third-party contract manufacturers ("CMOs"), to manufacture and supply our preclinical and clinical materials to be used during the development of our product candidates. We have established relationships with several CMOs, including Lonza Sales AG ("Lonza"). Effective September 2017, we entered into a development and manufacturing services agreement with Lonza, which agreement we have subsequently amended to add scope of work under this agreement. We refer to this agreement, as amended, as the DMSA or the Lonza agreement. Pursuant to the Lonza agreement, Lonza agreed to provide clinical development and manufacturing services with respect to certain of our biologic products on a fee-for-service basis.

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, GlaxoSmithKline, Merck, Roche (including Genentech, its wholly owned subsidiary), and Alector 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 and Lundbeck 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, Cytokinetics, Genentech and Mallinckrodt 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, Shire, Sangamo, RegenxBio 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 February 28, 2019, our owned and licensed patent portfolio includes over 800 patents and patent applications, including over 30 licensed U.S. issued patents, over 5 licensed U.S. pending patent applications, 7 owned U.S. issued patents, and over 30 owned U.S. pending patent applications, covering certain aspects of our proprietary technology, our product candidates, and related inventions and improvements. The patent portfolio also includes over 535 licensed patents issued in jurisdictions outside of the United States, over 50 licensed patent applications pending in jurisdictions outside of the United States, and over 140 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 ATVs and an issued U.S. patent and pending patent applications to other BBB platform technology. Furthermore, we own patent applications directed to our ATV:Tau, ATV:aSyn, ATV:TREM2, and ETV:IDS 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, our LRRK2 program, including DNL201, DNL151 and other related compounds, which are expected to expire in 2031, not including any patent term adjustments and any patent term extensions; and we 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 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 to the FDA of an IND, 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 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, unless the product also includes a non-orphan indication.

The FDA reviews all submitted NDAs and BLAs before it accepts them for filing, and may request additional information rather than accepting the NDA or BLA for filing. The FDA must make a decision on accepting an NDA or BLA for filing within 60 days of receipt. Once the submission is accepted for filing, the FDA begins an in-depth review of the NDA or BLA. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has ten months, from the filing date, in which to complete its initial review of a new molecular-entity NDA or original BLA and respond to the applicant, and six months from the filing date of a new molecular-entity NDA or original BLA designated for priority review. The FDA does not always meet its PDUFA goal dates for standard and priority NDAs or BLAs, and the review process 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 ensure 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 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. Recently enacted Clinical Trials Regulation EU No 536/2014 ensures that the rules for conducting clinical trials in the EU will be identical. In the meantime, Clinical Trials Directive 2001/20/EC continues to govern all clinical trials performed in the EU.

European Union Drug Review and Approval

In the European Economic Area ("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 European Medicines Agency ("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" (i.e., new formulations, such as extended release formulations) of solid oral dosage forms of branded products, as well as potentially impacting their rebate liability by modifying the statutory definition of AMP. The ACA also expanded the universe of Medicaid utilization subject to drug rebates by requiring pharmaceutical manufacturers to pay rebates on Medicaid managed care utilization and by enlarging the population potentially eligible for Medicaid drug benefits. The Centers for Medicare & Medicaid Services ("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.

Research and Development

We recognized $143.2 million, $74.5 million, and $75.7 million of research and development expenses in the years ended December 31, 2018, 2017 and 2016, respectively. The majority of these research and development expenses have related to the development of our RIPK1 and LRRK2 programs and our BBB platform technology.

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, 2018, we had approximately 179 employees, all of whom were full-time and around 145 of whom were engaged in research and development activities. Approximately two-thirds of our employees hold Ph.D. or M.D. degrees. Substantially all of our employees are located in South San Francisco, California. None of our employees is represented by a labor union or covered by a collective bargaining agreement.

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 clinical trials for our LRRK2 and RIPK1 programs and have not initiated clinical trials for any of our other current product candidates. To date, we have not initiated or completed a pivotal clinical trial, obtained marketing approval for any product candidates, manufactured a commercial scale product, or arranged for a third party to do so on our behalf, or conducted sales and marketing activities necessary for successful product commercialization. Our short operating history as a company makes any assessment of our future success and viability subject to significant uncertainty. We will encounter risks and difficulties frequently experienced by early-stage biopharmaceutical companies in rapidly evolving fields, and we have not yet demonstrated an ability to successfully overcome such risks and difficulties. If we do not address these risks and difficulties successfully, our business will suffer.

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

We have incurred net losses in each reporting period since our inception, including net losses of $36.2 million, $88.2 million, and $86.7 million for the years ended December 31, 2018, 2017 and 2016, respectively. As of December 31, 2018, we had an accumulated deficit of $227.9 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, or FDA, or foreign regulatory agencies, to perform studies in addition to those that we currently anticipate, or if there are any delays in any of our or our future collaborators' clinical trials or the development of any of our product candidates. Even if one or more of our product candidates is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate and ongoing compliance efforts.

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

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

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

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

As of December 31, 2018, we had $612.2 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 designate certain programs as core programs and others as seed programs. Together, 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 designation of each program as core or seed, 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 product candidates currently in our core programs, which are in the early stages of preclinical and clinical development. We cannot give any assurance that any of our product candidates will receive regulatory, including marketing, approval, which is necessary before they can be commercialized.

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

- our product candidates may not successfully complete preclinical studies or clinical trials;
- our drug delivery platform technology designed to deliver large molecule therapeutics across the BBB may not be clinically viable;
- a product candidate may on further study be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;
- our competitors may develop therapeutics that render our product candidates obsolete or less attractive;
- our competitors may develop platform technologies to deliver large molecule therapeutics across the BBB that render our platform technology obsolete or less attractive;

- the product candidates and BBB platform technology that we develop may not be sufficiently covered by intellectual property for which we hold exclusive rights;
- the product candidates and BBB platform technology that we develop may be covered by third parties' patents or other intellectual property or exclusive rights;
- the market for a product candidate may change so that the continued development of that product candidate is no longer reasonable or commercially attractive;
- a product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all;
- if a product candidate obtains regulatory approval, we may be unable to establish sales and marketing capabilities, or successfully market such approved product candidate, to gain market acceptance; and
- a product candidate may not be accepted as safe and effective by patients, the medical community or third-party payors, if applicable.

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

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

We have never completed a clinical development program. In the past, we have 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. We currently have one product candidate, DNL201, in a Phase 1b clinical study in Parkinson's disease patients with and without the genetic LRRK2 mutation, one product candidate, DNL747, in Phase 1b clinical studies in ALS and Alzheimer's disease patients, and one product candidate, DNL151, in a Phase 1 clinical trial in healthy volunteers. None of our product candidates have advanced into late-stage development or a pivotal clinical trial and it may be years before any such trial is initiated, if at all. Further, we cannot be certain that any of our product candidates will be successful in clinical trials. For instance, in 2016, we initiated a Phase 1 clinical trial in a former RIPK1 inhibitor product candidate, DNL104, which we subsequently discontinued based on liver test abnormalities in some clinical trial healthy volunteer participants. We may in the future advance product candidates into clinical trials and terminate such trials prior to their completion.

If any of our product candidates successfully complete clinical trials, we generally plan to seek regulatory approval to market our product candidates in the United States, the European Union, or EU, and in additional foreign countries where we believe there is a viable commercial opportunity. We have never commenced, compiled or submitted an application seeking regulatory approval to market any product candidate. We may never receive regulatory approval to market any product candidates even if such product candidates successfully complete clinical trials, which would adversely affect our viability. To obtain regulatory approval in countries outside the United States, we must comply with numerous and varying regulatory requirements of such other countries regarding safety, efficacy, chemistry, manufacturing and controls, clinical trials, commercial sales, pricing, and distribution of our product candidates. We may also rely on our collaborators or partners to conduct the required activities to support an application for regulatory approval, and to seek approval, for one or more of our product candidates. We cannot be sure that our collaborators or partners will conduct these activities or do so within the 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 investigational new drug application, or IND, or a clinical trial application, or CTA, will result in the FDA or European Medicines Agency, or EMA, as applicable, allowing clinical trials to begin in a timely manner, if at all. Moreover, even if these trials begin, issues may arise that could suspend or terminate such clinical trials. A failure of one or more clinical trials can occur at any stage of testing, and our future clinical trials may not be successful. Events that may prevent successful or timely initiation or completion of clinical trials include:

- inability to generate sufficient preclinical, toxicology, or other *in vivo* or *in vitro* data to support the initiation or continuation of clinical trials;
- delays in confirming target engagement, patient selection or other relevant biomarkers to be utilized in preclinical and clinical product candidate development;
- delays in reaching a consensus with regulatory agencies on study design;
- delays in reaching agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and clinical trial sites;
- delays in identifying, recruiting and training suitable clinical investigators;
- delays in obtaining required Institutional Review Board, or IRB, approval at each clinical trial site;

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

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

- difficulty collaborating with patient groups and investigators;

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

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

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

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

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

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

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

- transfer of manufacturing processes from our academic collaborators to larger-scale facilities operated by a CMO, or by us, and delays or failure by our CMOs or us to make any necessary changes to such manufacturing process; and

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

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

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

Our most advanced LRRK2 product candidate, DNL201, is in a Phase 1b clinical study 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 programs are DNL747, which is in Phase 1b clinical studies in ALS and Alzheimer's disease patients, and DNL151 which is currently in a Phase 1 clinical trial in healthy volunteers. In the nonclinical safety studies for DNL201, DNL747 and DNL151, toxicities were observed at high doses in rat and/or cynomolgus monkey above doses and exposures that will be tested in the clinic. We cannot assure you that DNL201, DNL747 and DNL151 or our other product candidates will not be subject to new, partial or full clinical holds in the future.

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

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

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

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

- the size and nature of the patient population;
- the patient eligibility criteria defined in the protocol, including biomarker-driven identification and/or certain highly-specific criteria related to stage of disease progression, which may limit the patient populations eligible for our clinical trials to a greater extent than competing clinical trials for the same indication that do not have biomarker-driven patient eligibility criteria;
- the size of the study population required for analysis of the trial’s primary endpoints;
- the proximity of patients to a trial site;
- the design of the trial;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience;
- competing clinical trials for similar therapies or targeting patient populations meeting our patient eligibility criteria;

- clinicians' and patients' perceptions as to the potential advantages and side effects of the product candidate being studied in relation to other available therapies and product candidates;
- our ability to obtain and maintain patient consents; and
- the risk that patients enrolled in clinical trials will not complete such trials, for any reason.

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

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

Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. The results of preclinical studies of our product candidates may not be predictive of the results of early-stage or later-stage clinical trials, and results of early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials. The results of clinical trials in one set of patients or disease indications may not be predictive of those obtained in another. In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial procedures set forth in protocols, differences in the size and type of the patient populations, changes in and adherence to the dosing regimen and other clinical trial protocols and the rate of dropout among clinical trial participants. 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.

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

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

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

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

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 CMOs will be able to manufacture the approved product to specifications acceptable to the FDA, EMA or other regulatory authorities, to produce it in sufficient quantities to meet the requirements for the potential launch of the product, or to meet potential future demand. Any of these challenges could delay completion of clinical trials, require bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our product candidate, impair commercialization efforts, increase our cost of goods, and have an adverse effect on our business, financial condition, results of operations and growth prospects.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Risks Related to Regulatory Approval and Other Legal Compliance Matters

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

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

Applications for our product candidates could fail to receive regulatory approval 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 and DNL151 are currently our only clinical stage product candidates. DNL201 and DNL747 have progressed to Phase 1b trials in patients in 2018, and DNL151 is in a Phase 1 trial in healthy volunteers. In trials to date, all three molecules have been well tolerated. Adverse events and other side effects may result from higher dosing, repeated dosing and/or longer-term exposure to DNL201, DNL747 and/or DNL151 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, or MAA. Accordingly, we and others with whom we work must continue to expend time, money, and effort in all areas of regulatory compliance, including manufacturing, production and quality control.

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

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

- issue warning letters that would result in adverse publicity;
- impose civil or criminal penalties;
- suspend or withdraw regulatory approvals;
- suspend any of our ongoing clinical trials;
- refuse to approve pending applications or supplements to approved applications submitted by us;
- impose restrictions on our operations, including closing our contract manufacturers' facilities;
- seize or detain products; 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. We plan to seek orphan drug designations for some product candidates and may be unable to obtain such designations.

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

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

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

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

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

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

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

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

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

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

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

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe, or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act;

- federal civil and criminal false claims laws and civil monetary penalty laws, including the False Claims Act, which impose criminal and civil penalties, including through civil “qui tam” or “whistleblower” actions, against individuals or entities from knowingly presenting, or causing to be presented, claims for payment or approval from Medicare, Medicaid, or other third-party payors that are false or fraudulent or knowingly making a false statement to improperly avoid, decrease or conceal an obligation to pay money to the federal government. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of these statutes or specific intent to violate them in order to have committed a violation;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their respective implementing regulations, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information without appropriate authorization;

- the federal Physician Payment Sunshine Act, created under the ACA, and its implementing regulations, which require manufacturers of drugs, devices, biologicals and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program to report annually to the U.S. Department of Health and Human Services under the Open Payments Program, information related to payments or other transfers of value made to physicians and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members;

- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers; and

- analogous state and foreign laws and regulations, such as state and foreign anti-kickback, false claims, consumer protection and unfair competition laws which may apply to pharmaceutical business practices, including but not limited to, research, distribution, sales and marketing arrangements as well as submitting claims involving healthcare items or services reimbursed by any third-party payer, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government that otherwise restricts payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to file reports with states regarding pricing and marketing information, such as the tracking and reporting of gifts, compensations and other remuneration and items of value provided to healthcare professionals and entities; and state and foreign laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

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

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

A wide variety of provincial, state, national, and international laws and regulations apply to the collection, use, retention, protection, disclosure, transfer and other processing of personal data. These data protection and privacy-related laws and regulations are evolving and may result in ever-increasing regulatory and public scrutiny and escalating levels of enforcement and sanctions. For example, the European Union General Data Protection Regulation, or GDPR, which became fully effective on May 25, 2018, imposes stringent data protection requirements and provides for penalties for noncompliance of up to the greater of Ä20 million or four percent of worldwide annual revenues. Additionally, California recently enacted legislation, the California Consumer Privacy Act, or 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, when it goes into effect on January 1, 2020. The CCPA was amended in September 2018, and it is unclear whether further modifications will be made to this legislation or how it will be interpreted. 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. 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.

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

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

Risks Related to Our Reliance on Third Parties

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

We anticipate seeking third-party collaborators for the research, development, and commercialization of certain of the product candidates we may develop. For example, we have collaborations with F-star, Takeda, 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. 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.

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 carries and may increase the risk that we will not have sufficient quantities of such materials, product candidates, or any medicines that we may develop and commercialize, or that such supply will not be available to us at an acceptable cost, which could delay, prevent, or impair our development or commercialization efforts.

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

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

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

Third-party manufacturers may not be able to comply with cGMP regulations or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in clinical holds on our trials, sanctions being imposed on us, including fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocations, seizures or recalls of product candidates or medicines, operating restrictions, and criminal prosecutions, any of which could significantly and adversely affect supplies of our medicines and harm our business, financial condition, results of operations and 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, core programs and product candidates, as well as other technologies that are important to our business. Given that the development of our technology and product candidates is at an early stage, our intellectual property portfolio with respect to certain aspects of our technology and product candidates is also at an early stage. For example, as of February 28, 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 core programs. We have filed or intend to file patent applications on these aspects of our technology and core product candidates; however, there can be no assurance that any such patent applications will issue as granted patents. Furthermore, in some cases, we have only filed provisional patent applications on certain aspects of our technology and product candidates and each of these provisional patent applications is not eligible to become an issued patent until, among other things, we file a non-provisional patent application within 12 months of the filing date of the applicable provisional patent application. Any failure to file a non-provisional patent application within this timeline could cause us to lose the ability to obtain patent protection for the inventions disclosed in the associated provisional patent applications. Furthermore, in some cases, we may not be able to obtain issued claims covering compositions relating to our BBB platform technology, core programs and product candidates, as well as other technologies that are important to our business, and instead may need to rely on filing patent applications with claims covering a method of use and/or method of manufacture for protection of such BBB platform technology, core programs, product candidates and other technologies. There can be no assurance that any such patent applications will issue as granted patents, and even if they do issue, such patent claims may be insufficient to prevent third parties, such as our competitors, from utilizing our technology. Any failure to obtain or maintain patent protection with respect to our BBB platform technology, core programs and product candidates could have a material adverse effect on our business, financial condition, results of operations and 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 non-disclosure and confidentiality agreements with parties who have access to confidential or patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, CROs, contract manufacturers, consultants, advisors, and other third parties, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. In addition, our ability to obtain and maintain valid and enforceable patents depends on whether the differences between our inventions and the prior art allow our inventions to be patentable over the prior art. Furthermore, publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we or our licensors were the first to make the inventions claimed in any of our owned or licensed patents or pending patent applications, or that we or our licensors were the first to file for patent protection of such inventions.

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

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

Moreover, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Even if patent applications we license or own currently or in the future issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us, or otherwise provide us with any competitive advantage. Any patents that we own or in-license may be challenged, narrowed, circumvented, or invalidated by third parties. Consequently, we do not know whether our BBB platform technology, product candidates or other technologies will be protectable or remain protected by valid and enforceable patents. Our competitors or other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner which could materially adversely affect our business, financial condition, results of operations and 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 United States Patent and Trademark Office, or USPTO, or become involved in opposition, derivation, revocation, reexamination, post-grant and *inter partes* review, or interference proceedings or other similar proceedings challenging our owned or licensed patent rights. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate or render unenforceable, our owned or in-licensed patent rights, allow third parties to commercialize our BBB platform technology, product candidates or other technologies and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. Moreover, we, or one of our licensors, may have to participate in interference proceedings declared by the USPTO to determine priority of invention or in post-grant challenge proceedings, such as oppositions in a foreign patent office, that challenge our or our licensor's priority of invention or other features of patentability with respect to our owned or in-licensed patents and patent applications. Such challenges may result in loss of patent rights, loss of exclusivity, or in patent claims being narrowed, invalidated, or held unenforceable, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our BBB platform technology, product candidates and other technologies. Such proceedings also may result in substantial cost and require significant time from our scientists and management, even if the eventual outcome is favorable to us. 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.

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

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

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

Furthermore, our owned and in-licensed patents may be subject to a reservation of rights by one or more third parties. For example, our license to certain intellectual property owned by Genentech is subject to certain research rights Genentech granted to third parties prior to our license agreement. In addition, certain of our in-licensed intellectual property relating to RIPK1 was funded in part by the U.S. government. As a result, the U.S. government may have certain rights to such intellectual property. When new technologies are developed with U.S. government funding, the U.S. government generally obtains certain rights in any resulting patents, including a non-exclusive license authorizing the U.S. government to use the invention or to have others use the invention on its behalf. The U.S. government's rights may also permit it to disclose the funded inventions and technology to third parties and to exercise march-in rights to use or allow third parties to use the technology we have licensed that was developed using U.S. government funding. The U.S. government may exercise its march-in rights if it determines that action is necessary because we fail to achieve practical application of the government-funded technology, or because action is necessary to alleviate health or safety needs, to meet requirements of federal regulations, or to give preference to U.S. industry. In addition, our rights in such inventions may be subject to certain requirements to manufacture products embodying such inventions in the United States in certain circumstances and if this requirement is not waived. Any exercise by the U.S. government of such rights or by any third party of its reserved rights could have a material adverse effect on our competitive position, business, financial condition, results of operations and 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, or the America Invents Act, enacted in September 2011, the United States transitioned to a first inventor to file system in which, assuming that other requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third party was the first to invent the claimed invention. A third party that files a patent application in the USPTO after March 2013, but before us could therefore be awarded a patent covering an invention of ours even if we had made the invention before it was made by such third party. This will require us to be cognizant going forward of the time from invention to filing of a patent application. Since patent applications in the United States and most other countries are confidential for a period of time after filing or until issuance, we cannot be certain that we or our licensors were the first to either (i) file any patent application related to our BBB platform technology, product candidates or other technologies or (ii) invent any of the inventions claimed in our or our licensor's patents or patent applications.

The America Invents Act also includes a number of significant changes that affect the way patent applications will be prosecuted and also may affect patent litigation. These include allowing third-party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent by USPTO administered post-grant proceedings, including post-grant review, *inter partes* review, and derivation proceedings. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in United States federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action. Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action. Therefore, the America Invents Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our owned or in-licensed patent applications and the enforcement or defense of our owned or in-licensed issued patents, all of which could have a material adverse effect on our business, financial condition, results of operations and 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. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. Third parties may raise claims challenging the validity or enforceability of our owned or in-licensed patents before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post-grant review, *inter partes* review, interference proceedings, derivation proceedings, and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). Such proceedings could result in the revocation of, cancellation of, or amendment to our patents in such a way that they no longer cover our BBB platform technology, product candidates or other technologies. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we or our licensing partners and the patent examiner were unaware during prosecution. If a third party were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our BBB platform technology, product candidates or other technologies. Such a loss of patent protection would have a material adverse impact on our business, financial condition, results of operations and 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 non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, CROs, contract manufacturers, consultants, advisors, and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants as well as train our employees not to bring or use proprietary information or technology from former employers to us or in their work, and remind former employees when they leave their employment of their confidentiality obligations. We cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology and processes. Despite our efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive, and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third party, our competitive position would be materially and adversely harmed.

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

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

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

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

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

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

Engaging in litigation to defend against third parties alleging that we have infringed, misappropriated or otherwise violated their patents or other intellectual property rights is very expensive, particularly for a company of our size, and time-consuming. Some of our competitors may be able to sustain the costs of litigation or administrative proceedings more effectively than we can because of greater financial resources. Patent litigation and other proceedings may also absorb significant management time. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings against us could impair our ability to compete in the marketplace. The occurrence of any of the foregoing could have a material adverse effect on our business, financial condition, 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, 2018, we had approximately 179 employees, all of whom were full-time. As our development plans and strategies develop, and as we transition into operating as a public company, we must add a significant number of additional managerial, operational, financial, and other personnel. Future growth will impose significant added responsibilities on members of management, including:

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

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

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

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

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, and affect our reputation.

Despite the implementation of security measures, our internal computer systems and those of our future CROs and other contractors and consultants may be vulnerable to damage from computer viruses and unauthorized access. As the cyber-threat landscape evolves, these attacks are growing in frequency, sophistication and intensity, and are becoming increasingly difficult to detect. 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. Although to our knowledge we 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. For example, the loss of clinical trial data from completed, ongoing or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Likewise, we rely on our third-party research institution collaborators for research and development of our product candidates and other third parties for the manufacture of our product candidates and to conduct clinical trials, and similar events relating to their computer systems could also have a material adverse effect on our business. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or systems, or inappropriate disclosure of confidential or proprietary information, including data related to our personnel, we could incur liability and the further development and commercialization of our product candidates could be delayed. There can be no assurance that we and our business counterparties will be successful in efforts to detect, prevent or fully recover systems or data from all breakdowns, service interruptions, attacks or breaches of systems that could adversely affect our business and operations and/or 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, CMOs, suppliers, and other contractors and consultants, could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics, and other natural or man-made disasters or business interruptions, for which we are partly uninsured. In addition, we rely on our third-party research institution collaborators for conducting research and development of our product candidates, and they may be affected by government shutdowns or withdrawn funding. The occurrence of any of these business disruptions could seriously harm our operations and financial condition and increase our costs and expenses. We rely on third-party manufacturers to produce and process our product candidates. Our ability to obtain clinical supplies of our product candidates could be disrupted if the operations of these suppliers are affected by a man-made or natural disaster or other business interruption.

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

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

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

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

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

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

As of December 31, 2018, we had federal net operating loss carryforwards of approximately $118.6 million, and federal research and development tax credit carryforwards of approximately $7.5 million which will begin to expire in 2035. Under Sections 382 and 383 of the United States Internal Revenue Code of 1986, as amended, or the Code, if a corporation undergoes an “ownership change” (generally defined as a greater than 50-percentage-point cumulative change (by value) in the equity ownership of certain stockholders over a rolling three-year period), the corporation’s ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change taxable income or taxes may be limited. As a result of our initial public offering ("IPO"), in December 2017 and recent private placements and other transactions that have occurred since our incorporation, we may have experienced such an ownership change. We may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership, some of which are outside our control. As a result, our ability to use our pre-change net operating loss carryforwards and other pre-change tax attributes to offset post-change taxable income or taxes may be subject to limitation.

Risks Related to Ownership of Our Common Stock

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

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

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

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

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

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

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

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

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

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

As of December 31, 2018, our directors, executive officers, holders of more than 5% of our outstanding stock and their respective affiliates beneficially own shares representing more than 50% of our outstanding common stock. As a result, these stockholders, if they act together, may significantly influence all matters requiring stockholder approval, including the election of directors and approval of significant corporate transactions. This concentration of ownership may have the effect of delaying or preventing a change in control of our company that our other stockholders may believe is in their best interests. This in turn could have a material adverse effect on our stock price and may prevent attempts by our stockholders to replace or remove the board of directors or management.

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

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

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

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

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

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

If we are unable to maintain effective internal controls, our business, financial position and results of operations 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, or the Exchange Act, including the requirements of SOX Section 404, which require annual management assessments of the effectiveness of our internal control over financial reporting. However, our auditors will not be required to formally attest to the effectiveness of our internal control over financial reporting pursuant to SOX Section 404 until we are no longer an emerging growth company if we continue to take advantage of the exemptions available to us through the JOBS Act.

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

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

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

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

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

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

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

In addition, Section 203 of the General Corporation Law of the State of Delaware, or DGCL, prohibits a publicly-held Delaware corporation from engaging in a business combination with an interested stockholder, generally a person which together with its affiliates owns, or within the last three years has owned, 15.0% 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, 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

We are currently occupying two facilities in South San Francisco, California, our former corporate headquarters where we lease approximately 38,000 square feet of office, research and development, engineering and laboratory space pursuant to a lease agreement which commenced on August 1, 2016, and our new corporate headquarters comprising 148,020 square feet of office, research and development, engineering and laboratory space. Our personnel is currently split between these two facilities. The lease for the former corporate headquarters will terminate when all personnel move to our new corporate headquarters, which is expected to be in April 2019. The corporate headquarters lease has a contractual term of ten years with an option to extend the lease term for a period of ten years. We believe that our existing and new 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. The following table sets forth for the periods indicated the high and low intraday sales price per share of our common stock as reported on The NASDAQ Global Select Market for the period indicated:

	High	Low
Year ended December 31, 2018		
First quarter	$ 25.79	$ 14.96
Second quarter	$ 22.99	$ 15.19
Third quarter	$ 21.89	$ 12.32
Fourth quarter	$ 22.40	$ 13.78
Year ended December 31, 2017		
Fourth quarter (from December 8, 2017)	$ 22.95	$ 14.72

Holders of Common Stock

As of March 5, 2019, there were 36 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.

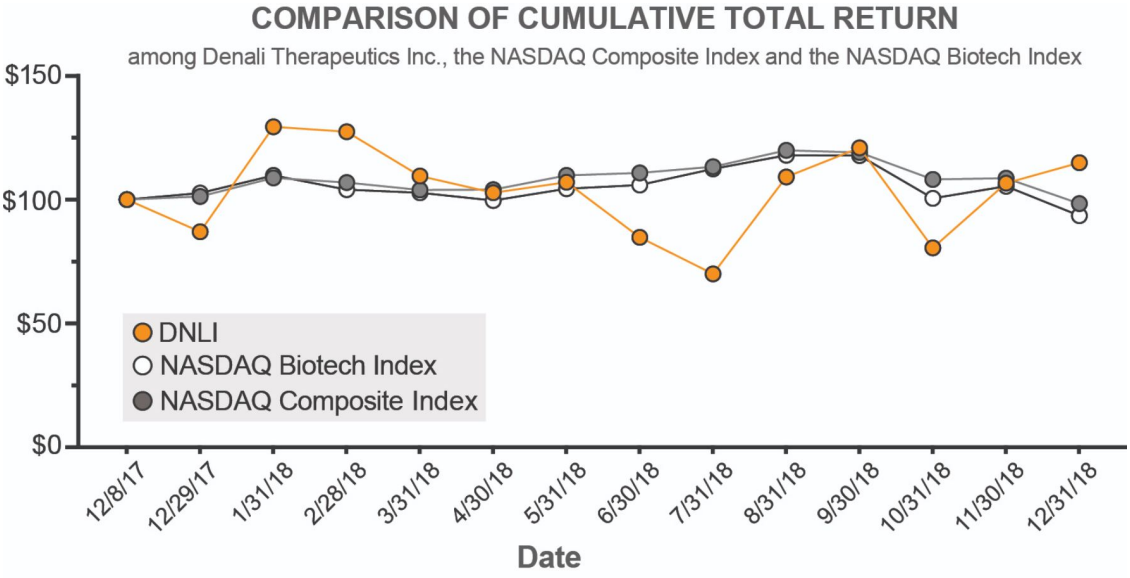
Dividend Policy

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.

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, 2018. 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.



	12/8/2017	12/31/2017	3/31/2018	6/30/2018	9/30/2018	12/31/18
Denali Therapeutics Inc.	$ 100.00	$ 87.03	$ 109.57	$ 84.66	$ 120.98	$ 114.97
NASDAQ Composite Index	100.00	101.37	103.99	110.87	119.09	98.49
NASDAQ Biotechnology Index	100.00	102.71	102.77	105.93	117.79	93.61

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.

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 have derived our selected consolidated statements of operations and comprehensive loss data for the years ended December 31, 2018, 2017, and 2016 and our selected consolidated balance sheets data as of December 31, 2018 and 2017 from our audited consolidated financial statements and related notes 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,		
	2018	2017	2016
	(In thousands, except share and per share amounts)		
Consolidated Statements of Operations and Comprehensive Loss Data:			
Collaboration revenue	$ 129,160	$ —	$ —
Operating expenses:			
Research and development	143,183	74,460	75,702
General and administrative	32,349	15,680	11,731
Total operating expenses	175,532	90,140	87,433
Loss from operations	(46,372)	(90,140)	(87,433)
Interest and other income, net	10,132	1,955	781
Net loss	(36,240)	(88,185)	(86,652)
Other comprehensive (loss) income:	(281)	5	(373)
Comprehensive loss	$ (36,521)	$ (88,180)	$ (87,025)
Net loss per share, basic and diluted [1]	$ (0.39)	$ (5.89)	$ (13.49)
Weighted average number of shares outstanding, basic and diluted [1]	92,621,991	14,964,144	6,424,720

1 See the consolidated statements of operations and Note 14 to our consolidated financial statements for further details on the calculation of net loss per share, basic and diluted, and the weighted-average number of shares used in the computation of the per share amounts.

	As of December 31,	
	2018	2017
Consolidated Balance Sheets Data:		
Cash, cash equivalents and marketable securities	$ 612,178	$ 466,976
Working capital [1]	448,050	395,443
Total assets	661,984	486,721
Total liabilities	115,139	20,925
Accumulated deficit	(227,937)	(191,697)
Total stockholders' equity	546,845	465,796

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

You should read the following discussion and analysis of our financial condition and results of operations 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:

- **Genetic Pathway Potential**: We select our therapeutic targets and disease pathways based on genes that, when mutated, cause, or are major risk factors for, neurodegenerative diseases, which we refer to as degenogenes;
- **Engineering Brain Delivery**: We engineer our product candidates to cross the BBB and act directly in the brain; 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 two programs in patient studies, two programs in IND-enabling studies, and an additional eight programs in various stages of preclinical development.

Our two clinical programs are our leucine-rich repeat kinase 2 ("LRRK2") inhibitor program to address Parkinson's disease and our receptor interacting serine/threonine protein kinase 1 ("RIPK1") inhibitor program to address Alzheimer's disease and amyotrophic lateral sclerosis ("ALS"). The two most advanced product candidates in our LRRK2 program, DNL201 and DNL151, are potent, selective and brain-penetrant small molecule LRRK2 inhibitor product candidates for Parkinson's disease. DNL201 is currently in a Phase 1b clinical study in Parkinson's disease patients with and without the genetic LRRK2 mutation. DNL151 is currently in a Phase 1 clinical trial in healthy volunteers in the Netherlands. The most advanced product candidate in our RIPK1 inhibitor program, DNL747, is a potent, selective and brain-penetrant small molecule RIPK1 inhibitor product candidate and is currently in Phase 1b clinical studies in ALS and Alzheimer's disease patients.

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

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

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

Key operational and financing milestones for the year ended December 31, 2018 and in 2019 to date include:

- In January 2018, we entered into the Takeda Collaboration Agreement pursuant to which we granted Takeda an option with respect to three of our programs to develop and commercialize, jointly with us, certain biologic products that are enabled by our BBB delivery technology and intended for the treatment of neurodegenerative disorders. Pursuant to this agreement, we received an upfront payment of $40.0 million in February 2018, as well as the first preclinical milestone payment of $5.0 million related to one of the programs in the agreement. Further, under the associated common stock purchase agreement (the "Stock Purchase Agreement"), we received proceeds of $110.0 million for the sale of 4,214,559 shares of our common stock which were issued on February 23, 2018;

- In February 2018, we submitted a CTA for DNL747, a RIPK1 inhibitor, to the Netherlands Health Authority, and we initiated a Phase 1 clinical trial of DNL747 in healthy volunteers in the Netherlands in March 2018;

- In May 2018, we exercised our right to nominate two additional Fcab (constant Fc-domains with antigen-binding activity) targets under the F-star Collaboration Agreement associated with our BBB platform technology, resulting in a one-time payment of $6.0 million to F-star Ltd;

- In May 2018, we also exercised our buy-out option to acquire all of the outstanding shares of F-star Gamma Limited, and subsequently changed the name of the entity to Denali BBB Holding Limited. We made initial exercise payments of, in the aggregate, $18.0 million, less the estimated net liabilities of F-star Gamma, which was $0.2 million. In addition, we are required under the buy-out option agreement and the F-star Gamma License to make future contingent payments to F-star Ltd 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;

- During the second quarter of 2018, one of our pending patent applications directed to the composition of matter of DNL151, a LRRK2 inhibitor, issued in the United States;

- During the second quarter of 2018, we achieved *in vivo* proof of concept for the ETV:IDS program in a mouse model of Hunter Syndrome;

- In October 2018, we confirmed that the first preclinical milestone was met for a second program under the Takeda Collaboration Agreement, triggering a milestone payment of $5.0 million, which we received in November 2018;

- In October 2018, we entered into the Collaboration Agreement with Genzyme Corporation, a wholly owned subsidiary of Sanofi S.A. ("Sanofi") to develop and commercialize therapeutic products to treat neurological and systemic inflammatory diseases by targeting and inhibiting RIPK1. 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 received an upfront fee of $125.0 million and is eligible to receive contingent milestone payments exceeding $1.1 billion. For RIPK1 inhibitors that measurably penetrate the blood-brain barrier, Denali and Sanofi will share select development costs and commercial profits and losses in the United States and China, while Denali will receive a royalty from Sanofi for other territories. For RIPK1 inhibitors that do not measurably penetrate the blood-brain barrier, Sanofi will pay all development costs and Denali will receive a royalty worldwide;

- In December 2018, we confirmed that the first preclinical milestone was met for the third program under the Takeda Collaboration Agreement, triggering a milestone payment of $5.0 million, which we received in February 2019;

- In December 2018, we announced the first patient dosed in our Phase 1b study of DNL201 in Parkinson’s disease patients with and without a genetic LRRK2 mutation; and

- 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.

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, and the proceeds from our IPO and payments received from our collaborations 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 $36.2 million, $88.2 million and $86.7 million for the years ended December 31, 2018, 2017 and 2016, respectively. As of December 31, 2018, we had an accumulated deficit of $227.9 million. We expect to continue to incur significant expenses and operating losses as we advance our LRRK2 and RIPK1 programs through 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 and ATV: TREM2 programs, and a third identified, but yet undisclosed discovery stage program. 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 ATV:BACE1/Tau with ATV:Tau.

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.

Takeda will be obligated to pay us up to an aggregate of $707.5 million upon achievement of certain clinical and regulatory milestone events if Takeda exercises its option for all three collaboration programs. Furthermore, Takeda will 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.

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 $600.0 million in clinical and regulatory milestone payments for CNS Products and $495.0 million in clinical, regulatory and commercial milestone payments for Peripheral Products.

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.

F-star

In August 2016, we entered into a License and Collaboration Agreement ("F-star Collaboration Agreement") with F-star. The goal of the collaboration is the development of Fcabs to enhance delivery of therapeutics across the BBB into the brain. The collaboration leverages F-star's modular antibody technology and our expertise in the development of therapies for neurodegenerative diseases. 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 become a wholly-owned subsidiary of the Company, which was subsequently renamed 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 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 is 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 of $447.0 million in the aggregate upon the achievement of certain defined preclinical, clinical, regulatory and commercial milestones. The amount of the contingent payments varies based on whether F-star delivers an Fcab (constant Fc-domains with antigen-binding activity) that meets pre-defined criteria and whether the Fcab has been identified solely by us or solely by F-star Ltd. or jointly by us and F-star Ltd.

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 the upfront purchase price less estimated net liabilities acquired of $17.8 million, and $6.0 million for the nomination of two additional Accepted Fcab Targets, as research and development expense in the year ended December 31, 2018 . The upfront option fee of $0.5 million previously included within other non-current assets was also recognized as research and development expense in the same period. We recognized an additional $0.7 million, $1.1 million and $0.3 million of research and development expense related to the funding of F-star research costs for the years ended December 31, 2018, 2017 and 2016, 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, we paid an upfront fee of $8.5 million and a technology transfer fee of $1.5 million, both of which are included in research and development expense for the year ended December 31, 2016 as there is no alternative future use of the rights acquired in other research and development projects.

We may owe Genentech milestone payments upon the achievement of certain development, regulatory, and commercial milestones, up to a maximum of $315.0 million in the aggregate, as well as royalties on net sales of licensed products ranging from low to high single-digit percentages, with the exact royalty rate dependent on various factors, including (i) whether the compound incorporated in the relevant licensed product is a Genentech-provided compound or a compound acquired or developed by us, (ii) the date a compound was first discovered, derived or optimized by us, (iii) the existence of patent rights covering the relevant licensed product in the relevant country, (iv) the existence of orphan drug exclusivity covering a licensed product that is a Genentech-provided compound and (v) the level of annual net sales of the relevant licensed product. We also have the right to credit a certain amount of third-party royalty and milestone payments against royalty and milestone payments owed to Genentech, up to a maximum reduction of fifty percent. The first clinical milestone of $2.5 million became due upon first patient dosing in the Phase 1 clinical trial for DNL201 and was recognized as research and development expense during the year ended December 31, 2017.

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

Components of Operating Results

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 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 CROs, preclinical testing organizations, CMOs, academic and non-profit institutions and consultants;
    - expenses to acquire technologies to be used in research and development that have not reached technological feasibility and have no alternative future use;
    - fees related to our license and collaboration agreements;

- personnel related expenses, including salaries, benefits and non-cash stock-based compensation expense; and
- other expenses, which include direct and allocated expenses for laboratory, facilities and other costs.

A portion of our research and development expenses are direct external expenses, which we track on a program-specific basis once a program has commenced 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 depreciation and lab consumables.

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

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

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

General and Administrative

General and administrative expenses include personnel related expenses, such as salaries, benefits, travel and non-cash stock-based compensation expense, expenses for outside professional services and allocated expenses. Outside professional services consist of legal, accounting and audit services and other consulting fees. Allocated expenses consist of rent expenses related to our office and research and development facility not otherwise included in research and development expenses.

We expect to incur additional expenses as a result of operating as a public company, including expenses related to compliance with the rules and regulations of the SEC and those of any national securities exchange on which our securities are traded, additional insurance expenses, investor relations activities and other administrative and professional services. We also expect to increase our administrative headcount as we advance our product candidates through clinical development, which will also likely require us to increase our general and administrative expenses.

Interest and Other Income, Net

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

Results of Operations

Comparison of the years ended December 31, 2018 and 2017

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

	Year Ended December 31,		Change	
	2018	2017	$	%
Collaboration revenue	$ 129,160	$ —	$ 129,160	*
Operating expenses:				
Research and development	143,183	74,460	68,723	92 %
General and administrative	32,349	15,680	16,669	106
Total operating expenses	175,532	90,140	85,392	95
Loss from operations	(46,372)	(90,140)	43,768	(49)
Interest and other income, net	10,132	1,955	8,177	418
Net loss	$ (36,240)	$ (88,185)	$ 51,945	(59) %

- Percentage is not meaningful

Collaboration Revenue. Collaboration Revenue was $129.2 million for the year ended December 31, 2018, with no revenue recognized for the year ended December 31, 2017. The increase was due to $123.5 million of revenue recognized under our Sanofi Collaboration Agreement and $5.7 million of revenue recognized under our Takeda Collaboration Agreement.

Research and development expenses. Research and development expenses were $143.2 million for the year ended December 31, 2018 compared to $74.5 million for the year ended December 31, 2017.

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

	Year Ended December 31,		Change	
	2018	2017	$	%
LRRK2 program external expenses[1]	$ 13,167	$ 13,515	$ (348)	(3) %
RIPK1 program external expenses	13,452	10,426	3,026	29
BBB platform external expenses [2]	29,827	3,294	26,533	805
Other external research and development expenses	21,232	10,428	10,804	104
Personnel related expenses [3]	41,923	23,466	18,457	79
Other unallocated research and development expenses	23,582	13,331	10,251	77
Total research and development expenses	$ 143,183	$ 74,460	$ 68,723	92 %

1 The amount for the year ended December 31, 2017 includes a milestone payment of $2.5 million under the license agreement with Genentech.
2 The amount for the year ended December 31, 2018 includes the upfront purchase price less estimated net liabilities acquired of $17.8 million, and transaction costs of $1.9 million in relation to our acquisition of F-star Gamma Limited, and the $6.0 million one-time payment made to F-star Ltd to nominate two additional Fcab targets under the F-star Collaboration Agreement.
3 Personnel-related expenses include stock-based compensation expense of $10.1 million and $2.9 million for the years ended December 31, 2018 and 2017, respectively, reflecting an increase of $7.2 million.

The increase in total research and development expenses of $68.7 million for the year ended December 31, 2018 compared to the year ended December 31, 2017 was primarily attributable to a $26.5 million increase in BBB platform external expenses, the majority of which related to expense associated with the acquisition of F-star Gamma Limited as well as the nomination of two additional Fcab targets under the F-star Collaboration Agreement. Personnel-related expenses increased by 18.5 million primarily consisting of a $11.2 million increase in salaries and related expenses attributable to an increase in our research and development headcount, and a $7.2 million increase in stock-based compensation expense attributable to new options granted at higher valuations subsequent to the IPO, and an increase in our research and development headcount. Additionally, there was a $10.8 million increase in other external research and development expenses, which reflects our increased investment in growing and developing our pipeline, and an increase in other unallocated research and development expenses of $10.3 million, which was primarily due to an increase in facilities related expenses of $8.2 million due to higher rent expense associated with the Headquarters Lease Amendment and an increase in lab consumable expenses of $1.6 million attributable to increases in research and development headcount. Further, RIPK1 program external expenses increased by $3.0 million as DNL747 moved into clinical trials in March 2018. These increases were partially offset by a $0.3 million decrease in LRRK2 program external expenses, primarily due to the milestone payment of $2.5 million under the license agreement with Genentech included in the year ended December 31, 2017, which offset an otherwise increase in spending in the program related to increased clinical trial activity.

General and administrative expenses. General and administrative expenses were $32.3 million for the year ended December 31, 2018 compared to $15.7 million for the year ended December 31, 2017, including stock-based compensation expense of $8.7 million and $1.6 million in the years ended December 31, 2018 and 2017, respectively. The increase of $16.7 million was primarily attributable to the $7.1 million increase in stock-based compensation expense due to new options granted at higher exercise prices subsequent to the IPO and an increase in our general and administrative headcount, a $3.6 million increase in facilities and other general and administrative costs primarily due to higher rent expense associated with the Headquarters Lease Amendment and an increase in our general and administrative headcount, a $3.4 million increase in other personnel-related expenses due to an increase in our general and administrative headcount, and a $2.6 million increase in legal expenses and other professional services to support our ongoing operations as a public company.

Interest and other income, net. Interest income, net was $10.1 million for the year ended December 31, 2018 compared to $2.0 million for the year ended December 31, 2017. The increase of $8.1 million reflects that the marketable securities balances were higher in 2018 than in 2017, and higher yields on securities due to a rising interest rate environment in the year ended December 31, 2018 compared to the prior year.

Comparison of the years ended December 31, 2017 and 2016

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

	Year Ended December 31,		Change	
	2017	2016	$	%
Operating expenses:				
Research and development	$ 74,460	$ 75,702	$ (1,242)	(2) %
General and administrative	15,680	11,731	3,949	34
Total operating expenses	90,140	87,433	2,707	3
Loss from operations	(90,140)	(87,433)	(2,707)	3
Interest and other income, net	1,955	781	1,174	150
Net Loss	$ (88,185)	$ (86,652)	$ (1,533)	2 %

Research and development expenses. Research and development expenses were $74.5 million for the year ended December 31, 2017 compared to $75.7 million for the year ended December 31, 2016.

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

	Year Ended December 31,		Change	
	2017	2016	$	%
LRRK2 program external expenses [1]	$ 13,515	$ 16,770	$ (3,255)	(19) %
RIPK1 program external expenses [2]	10,426	19,106	(8,680)	(45)
BBB platform external expenses [3]	3,294	8,016	(4,722)	(59)
Other external research and development expenses	10,428	8,020	2,408	30
Personnel related expenses [4]	23,466	14,974	8,492	57
Other unallocated research and development expenses	13,331	8,816	4,515	51
Total research and development expenses	$ 74,460	$ 75,702	$ (1,242)	(2) %

1 Payments under the license agreement with Genentech for a milestone payment of $2.5 million and an upfront payment and technology transfer fee totaling $10.0 million are included in the amounts for the year ended December 31, 2017 and 2016, respectively.
2 The amount for the year ended December 31, 2016 includes $5.3 million in expenses related to contingent and initial stock consideration, respectively, both issued in connection with our acquisition of Incro Pharmaceuticals, Inc. ("Incro").
3 The amount for the year ended December 31, 2016 includes $5.5 million in expenses related to a payment made under our license and collaboration agreement with F-star.
4 Personnel related expenses include stock-based compensation expense of $2.9 million and $2.1 million for the years ended December 31, 2017 and 2016 respectively, reflecting an increase of $0.8 million.

The decrease in total research and development expenses of $1.2 million was primarily attributable to a $8.7 million decrease in RIPK1 program external expenses and a $4.7 million decrease in BBB platform external expenses. The decrease in RIPK1 is primarily due to the $5.3 million expense associated with the issuance of our common stock to former shareholders of Incro Pharmaceuticals ("Incro") as contingent consideration for our acquisition of Incro in the year ended December 31, 2016, as well as the termination of the Phase 1 clinical trial for DNL104 in April 2017. The decrease in BBB platform expenses is primarily due to the payment of $5.5 million made under our license and collaboration agreement with F-star in the year ended December 31, 2016, partially offset by increased expenses incurred in the year ended December 31, 2017 to support preclinical development of our BBB platform.

These decreases in external research and development expenses were partially offset by a $8.5 million increase in personnel related expenses due to an increase in our research and development headcount and a $4.5 million increase in other unallocated research and development expenses. The increase in other unallocated research and development expenses consisted of an increase in lab consumable expenses of $2.3 million and an increase in facilities related expenses of $2.5 million, attributable to increases in research and development headcount and the move to our new headquarters in August 2016, which allowed us to significantly increase our lab space capacity.

General and administrative expenses. General and administrative expenses were $15.7 million for the year ended December 31, 2017 compared to $11.7 million for the year ended December 31, 2016. The increase of $3.9 million was primarily attributable to a $1.9 million increase in personnel related expenses due to an increase in our general and administrative headcount, a $1.3 million increase in patent expenses and professional services to support our ongoing operations and $0.2 million related to increased facilities expenses attributable to general and administrative expenses resulting from the move to our new headquarters in August 2016.

Interest and other income, net. Interest and other income, net was $2.0 million for the year ended December 31, 2017 compared to $0.8 million for the year ended December 31, 2016. The increase of $1.2 million reflects that the marketable securities balances were higher in 2017 than in 2016, and higher yields on securities due to a rising interest rate environment in the year ended December 31, 2017 compared to prior years.

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 and payments received from our collaborations 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.

In February 2018, pursuant to the Takeda Collaboration Agreement, we received a $40.0 million upfront payment and a $5.0 million preclinical milestone payment. Two further $5.0 million preclinical milestone payments were received in November 2018 and February 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.

In November 2018, pursuant to the Sanofi Collaboration Agreement, we received an upfront payment of $125.0 million.

As of December 31, 2018, we had cash, cash equivalents and marketable securities in the amount of $612.2 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 continue the development of, and seek regulatory approvals for, our product candidates, and begin to commercialize any approved products. Further, we expect general and administrative expenses to increase as we will now incur additional costs associated with operating as a public company. We are subject to all of the risks typically related to the development of new product candidates, and we may encounter unforeseen expenses, difficulties, complications, delays and other unknown factors that may adversely affect our business. We anticipate that we will need substantial additional funding in connection with our continuing operations.

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 $227.9 million through December 31, 2018. We expect to incur substantial additional losses in the future as we conduct and expand our research and development activities. We believe that our existing cash, cash equivalents and marketable securities will be sufficient to enable us to fund our projected operations through at least the next 12 months. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we currently expect. Our future funding requirements will depend on many factors, including:

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

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

Cash Flows

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

	Year Ended December 31,		
	2018	2017	2016
Net cash provided by (used in) operating activities	$ 50,116	$ (76,635)	$ (71,908)
Net cash used in investing activities	(287,422)	(41,166)	(219,004)
Net cash provided by financing activities	97,019	296,323	300,476
Net (decrease) increase in cash, cash equivalents and restricted cash	$ (140,287)	$ 178,522	$ 9,564

Net Cash Provided By (Used In) Operating Activities

During the year ended December 31, 2018, cash provided by operating activities was $50.1 million, which consisted of a net loss of $36.2 million, adjusted by non-cash adjustments of $23.5 million and cash provided by changes in our operating assets and liabilities of $62.9 million. The non-cash adjustments consisted primarily of stock-based compensation expense of $18.8 million and depreciation expense of $7.4 million, partially offset by net amortization of premiums and discounts on marketable securities of $2.7 million. The change in our operating assets and liabilities was primarily due to an increase of $68.8 million in the contract liability related to the Takeda Collaboration Agreement and Sanofi Collaboration Agreement, and an increase of $9.1 million in accrued and other current liabilities, partially offset by an increase in prepaid expenses and other assets of $18.3 million due to upfront payments in various research and other collaborations, including a patient recruitment agreement with Centogene.

During the year ended December 31, 2017, cash used in operating activities was $76.6 million, which consisted of a net loss of $88.2 million, adjusted by non-cash adjustments of $8.2 million and cash provided by changes in our operating assets and liabilities of $3.3 million. The non-cash adjustments consisted primarily of stock-based compensation expense of $4.4 million and depreciation expense of $3.1 million. The change in our operating assets and liabilities was primarily due to an increase of $3.6 million in accrued and other current liabilities, mainly attributable to an increase in accrued compensation due to our continued growth, and accruals for legal expenses incurred in connection with our IPO and negotiation of the Collaboration Agreement with Takeda.

During the year ended December 31, 2016, cash used in operating activities was $71.9 million, which consisted of a net loss of $86.7 million, adjusted by non-cash adjustments of $10.0 million and cash provided by changes in our operating assets and liabilities of $4.7 million. The non-cash adjustments consisted primarily of the expense recognized for the fair value of our common stock issued in connection with the acquisition of Incro of $5.3 million and stock-based compensation expense of $3.0 million. The change in our operating assets and liabilities was primarily due to an increase of $5.4 million of accrued and other liabilities. Our accrued liabilities increased due to employee bonuses and general business expenses, reflective of our increased headcount and expenses. This was partially offset by an increase in restricted cash of $0.5 million associated with the lease for our new headquarters and an increase of $0.5 million in prepaid expenses and other assets mainly associated with prepayments made for ongoing research and development being conducted by third-party service providers.

Net Cash Used In Investing Activities

During the year ended December 31, 2018, cash used in investing activities was $287.4 million, which consisted of $557.9 million of purchases of marketable securities and $3.4 million of capital expenditures to purchase property and equipment, partially offset by $273.9 million in proceeds from the maturity of marketable securities.

During the year ended December 31, 2017, cash used in investing activities was $41.2 million, which consisted of $179.8 million of purchases of marketable securities and $2.9 million of capital expenditures to purchase property and equipment, partially offset by $141.5 million in proceeds from the maturity of marketable securities.

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

Net Cash Provided By Financing Activities

During the year ended December 31, 2018, cash provided by financing activities was $97.0 million, which consisted of the $94.4 million market value of the 4,214,559 shares of common stock issued to Takeda in February 2018 under the Stock Purchase Agreement, and $4.0 million of proceeds from the exercise of options to purchase common stock and issuance of ESPP shares. These amounts were partially offset by $1.4 million for payments of issuance costs related to the issuance of common and preferred stock.

During the year ended December 31, 2017, cash provided by financing activities was $296.3 million, which primarily consisted of net proceeds from our IPO of $265.6 million and net proceeds from issuance of shares of our Series B-2 convertible preferred stock of $30.0 million.

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

Off-Balance Sheet Arrangements

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

Contractual Obligations and Commitments

The following table summarizes our contractual obligations as of December 31, 2018 (in thousands):

	Total	Less Than 1 Year	1-3 Years	3-5 Years	More Than 5 Years
Operating lease obligations [1]	$ 105,100	$ 4,941	$ 18,813	$ 20,464	$ 60,882
Obligations under license and other contractual agreements [2]	15,227	14,267	120	160	680
Total contractual obligations [3]	$ 120,327	$ 19,208	$ 18,933	$ 20,624	$ 61,562

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 headquarters lease (the "Headquarters Lease Amendment") to relocate and expand our headquarters to 148,020 rentable square feet in a to-be-constructed building in South San Francisco, California (the "New Premises"). The Headquarters Lease Amendment has a contractual term of ten years from the legal commencement date, which is the later of February 1, 2019 or the date that the premises are ready for occupancy. For accounting purposes, the lease commencement date was determined to be August 1, 2018, which was the date on which we 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.

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

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 Lonza agreement will expire on September 6, 2022.

As of December 31, 2018, we had several purchase orders for biological product development and manufacturing costs totaling $24.7 million. The activities under these purchase orders are expected to be completed by November 2024. During the year ended December 31, 2018, we incurred costs of $3.9 million and made payments of $3.4 million for the development and manufacturing services rendered under the agreement. As of December 31, 2018, we had total non-cancellable purchase commitments of $14.0 million under the DMSA.

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 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 generally accepted accounting principles in the United States ("GAAP"). The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the consolidated financial statements, as well as the reported expenses incurred during the reporting periods. Our estimates are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. While our significant accounting policies are described in more detail in the notes to our consolidated financial statements included elsewhere in this 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 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: nonrefundable, up-front license fees; development, regulatory and commercial milestone payments; payments for manufacturing supply services; and royalties on net sales of licensed products. Each of these payments results in license, collaboration and other 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 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 stand-alone selling prices 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, CMOs, academic and non-profit institutions and consultants; costs to acquire technologies to be used in research and development that have not reached technological feasibility and have no alternative future use; license fees; and other expenses, which include direct and allocated expenses for laboratory, facilities and other costs.

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

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

Stock-Based Compensation

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

We estimate the fair value of stock options granted to our employees and directors on the grant date, and rights to acquire stock granted under our Employee Stock Purchase Plan ("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 following methods:

- *Current Value Method.* Under the Current Value Method ("CVM"), our value is determined based on our balance sheet. This value is then first allocated based on the liquidation preference associated with preferred stock issued as of the valuation date, and then any residual value is assigned to the common stock.

- *Option-Pricing Method.* Under the option-pricing method ("OPM"), shares are valued by creating a series of call options with exercise prices based on the liquidation preferences and conversion terms of each equity class. The estimated fair values of the preferred and common stock are inferred by analyzing these options.

- *Probability-Weighted Expected Return Method.* The probability-weighted expected return method ("PWERM"), is a scenario-based analysis that estimates value per share based on the probability-weighted present value of expected future investment returns, considering each of the possible outcomes available to us, as well as the economic and control rights of each share class.

Our 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.

Stock-based compensation expense was $18.8 million, $4.4 million and $3.0 million for the years ended December 31, 2018, 2017, and 2016, respectively. As of December 31, 2018, we had $57.6 million of total unrecognized stock-based compensation expenses which we expect to recognize over a weighted-average period of 3.0 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.

JOBS Act

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

Subject to certain conditions set forth in the JOBS Act, as an emerging growth company, we intend to rely on certain exemptions and reduced reporting requirements provided by the JOBS Act, including those relating to (i) providing an auditor's attestation report on our system of internal control over financial reporting pursuant to Section 404(b) of the Sarbanes-Oxley Act and (ii) complying with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements, known as the auditor discussion and analysis.

We will remain an emerging growth company until the earliest of (i) the last day of our first fiscal year in which we have total annual gross revenues of $1.07 billion or more, (ii) the date on which we are deemed to be a “large accelerated filer” under the rules of the SEC with at least $700.0 million of outstanding equity securities held by non-affiliates, (iii) the date on which we have issued more than $1.0 billion in non-convertible debt securities during the previous three years, or (iv) December 31, 2022.

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 $612.2 million as of December 31, 2018, which consisted primarily of money market funds and marketable securities, largely composed of investment grade, short to intermediate term fixed income securities.

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

Foreign Currency Sensitivity

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

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

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

As of December 31, 2018, we had open forward foreign currency exchange contracts with notional amounts of $9.2 million. A hypothetical 10.0% strengthening in foreign currency compared with the U.S. dollar at December 31, 2018 would have resulted in an increase in the value received over the remaining life of these contracts of approximately $0.9 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.
Index to Consolidated Financial Statements

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, 2018 and 2017, 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, 2018, 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, 2018 and 2017, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2018, in conformity with U.S. generally accepted accounting principles.

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 Public Company Accounting Oversight Board (United States) (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. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

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.

/s/ Ernst & Young LLP

We have served as the Company’s auditor since 2015.
Redwood City, California
March 12, 2019

Denali Therapeutics Inc.

Consolidated Balance Sheets
(In thousands, except share amounts)

	December 31, 2018	December 31, 2017
Assets		
Current assets:		
Cash and cash equivalents	$ 77,123	$ 218,375
Short-term marketable securities	387,174	187,851
Prepaid expenses and other current assets	16,539	3,381
Total current assets	480,836	409,607
Long-term marketable securities	147,881	60,750
Property and equipment, net	25,162	14,923
Other non-current assets	8,105	1,441
Total assets	$ 661,984	$ 486,721
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 1,891	$ 2,716
Accrued liabilities	8,520	5,364
Accrued compensation	9,952	5,166
Contract liability	11,427	—
Deferred rent	616	855
Other current liabilities	380	63
Total current liabilities	32,786	14,164
Contract liability, less current portion	57,350	—
Deferred rent, less current portion	24,532	6,294
Other non-current liabilities	471	467
Total liabilities	115,139	20,925
Commitments and contingencies (Note 9)		
Stockholders' equity:		
Convertible preferred stock, $0.01 par value; 40,000,000 shares authorized as of December 31, 2018 and December 31, 2017; 0 shares issued and outstanding as of December 31, 2018 and December 31, 2017	—	—
Common stock, $0.01 par value; 400,000,000 shares authorized as of December 31, 2018 and December 31, 2017; 94,662,435 shares and 87,480,362 shares issued and outstanding as of December 31, 2018 and December 31, 2017, respectively	1,273	1,201
Additional paid-in capital	774,158	656,660
Accumulated other comprehensive loss	(649)	(368)
Accumulated deficit	(227,937)	(191,697)
Total stockholders' equity	546,845	465,796
Total liabilities and stockholders' equity	$ 661,984	$ 486,721

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,		
	2018	2017	2016
Collaboration revenue	$ 129,160	$ —	$ —
Operating expenses:			
Research and development	143,183	74,460	75,702
General and administrative	32,349	15,680	11,731
Total operating expenses	175,532	90,140	87,433
Loss from operations	(46,372)	(90,140)	(87,433)
Interest and other income, net	10,132	1,955	781
Net loss	(36,240)	(88,185)	(86,652)
Other comprehensive (loss) income:			
Net unrealized (loss) gain on marketable securities, net of tax	(281)	5	(373)
Comprehensive loss	$ (36,521)	$ (88,180)	$ (87,025)
Net loss per share, basic and diluted	$ (0.39)	$ (5.89)	$ (13.49)
Weighted average number of shares outstanding, basic and diluted	92,621,991	14,964,144	6,424,720

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, 2015	12,197,880	$ 48,308	4,260,560	$ 170	$ 1,056	$ —	$ (16,860)	$ (15,634)
Issuance of series A-1 convertible preferred stock, net of issuance costs of $23	33,916,543	135,643	—	—	—	—	—	—
Issuance of series A-2 convertible preferred stock, net of issuance costs of $7	4,361,527	34,885	—	—	—	—	—	—
Issuance of series B-1 convertible preferred stock, net of issuance costs of $153	8,124,365	129,837	—	—	—	—	—	—
Issuance of common stock as contingent consideration in asset acquisition	—	—	945,880	38	5,242	—	—	5,280
Issuance of common stock upon exercise of stock options	—	—	162,665	6	105	—	—	111
Vesting of early exercised common stock	—	—	239,580	10	153	—	—	163
Vesting of restricted stock awards	—	—	2,988,631	120	(120)	—	—	—
Stock-based compensation	—	—	—	—	2,951	—	—	2,951
Net loss	—	—	—	—	—	—	(86,652)	(86,652)
Other comprehensive loss	—	—	—	—	—	(373)	—	(373)
Balance at December 31, 2016	58,600,315	348,673	8,597,316	344	9,387	(373)	(103,512)	(94,154)
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

See accompanying notes to consolidated financial statements.

Denali Therapeutics Inc.

Consolidated Statements of Cash Flows
(In thousands)

	Year Ended December 31,		
	2018	2017	2016
Operating activities			
Net loss	$ (36,240)	$ (88,185)	$ (86,652)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation and amortization	7,415	3,082	1,469
Stock-based compensation expense	18,791	4,409	2,951
Net amortization of premiums and (discounts) on marketable securities	(2,705)	753	304
(Gain) loss on disposal of property and equipment	(36)	1	3
Fair value of common stock issued in connection with asset acquisition	—	—	5,280
Changes in operating assets and liabilities:			
Prepaid expenses and other assets	(18,290)	73	(533)
Accounts payable	(526)	207	161
Accrued and other current liabilities	9,113	3,578	5,357
Deferred rent	3,438	—	—
Contract liability	68,777	—	—
Other non-current liabilities	379	(553)	(248)
Net cash provided by (used in) operating activities	50,116	(76,635)	(71,908)
Investing activities			
Purchase of marketable securities	(557,930)	(179,789)	(226,370)
Purchase of property and equipment	(3,393)	(2,875)	(6,134)
Purchase of other investments	—	—	(500)
Maturities and sales of marketable securities	273,901	141,498	14,000
Net cash used in investing activities	(287,422)	(41,166)	(219,004)
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 common stock options	3,999	733	111
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	300,365
Net cash provided by financing activities	97,019	296,323	300,476
Net (decrease) increase in cash and cash equivalents	(140,287)	178,522	9,564
Cash, cash equivalents and restricted cash at beginning of year	218,910	40,388	30,824
Cash, cash equivalents and restricted cash at end of year	$ 78,623	$ 218,910	$ 40,388
Supplemental disclosures of cash flow information			
Tenant improvements provided by the landlord	$ 14,561	$ —	$ —
Property and equipment purchases accrued but not yet paid	$ 335	$ 103	$ 233
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 Company convertible preferred stock converted into 60,365,020 shares of common stock. The related carrying value of $378.6 million was reclassified to common stock and additional paid-in capital. 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 on consolidation. For the Company's subsidiary, the functional currency has been determined to be the U.S. dollar. 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, and have not been material.

Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires the Company to make certain estimates, judgments and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the consolidated financial statements, as well as the reported amounts of expenses during the reporting period. Actual results could differ from those estimates, and such differences could be material to the consolidated financial position and 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 and marketable securities. 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, 2018 and 2017, the Company had no off-balance sheet concentrations of credit risk.

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

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

Segments

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

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 and Cash Equivalents

The Company considers all highly liquid investments with original maturities of 90 days or less at the date of purchase to be cash and cash equivalents. Cash equivalents are stated at fair value.

Marketable Securities

The Company generally invests its excess cash in money market funds and investment grade short to intermediate-term fixed income securities. Such investments are included in cash and cash equivalents, short-term marketable securities, or long-term marketable securities on the balance sheets, are considered available-for-sale, and reported at fair value with unrealized gains and losses included as a component of stockholders' equity (deficit). 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.

Restricted Cash

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

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 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 sheet 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.

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.

Deferred Rent

Certain of the Company's operating lease agreements include scheduled rent escalations over the lease term, as well as tenant improvement allowances. Rent expense is charged ratably over the life of the lease. Deferred rent consists of the difference between cash payments and the recognition of rent expense on a straight-line basis for the buildings the Company occupies. Tenant improvement allowances are recorded as a deferred rent liability and are amortized on a straight-line basis over the term of the lease as a reduction to rent expense.

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: nonrefundable, up-front license fees; development, regulatory and commercial milestone payments; payments for manufacturing supply services; and royalties on net sales of licensed products. Each of these payments results in license, collaboration and other 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 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 stand-alone selling prices 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.

The Company granted restricted stock awards that vest in conjunction with certain performance conditions to certain key employees and directors. At each reporting date, the Company is required to evaluate whether achievement of the performance conditions is probable. Compensation expense is recorded over the appropriate service period based upon the Company's assessment of accomplishing each performance provision.

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 Loss

Comprehensive loss includes 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 February 2016, the Financial Accounting Standards Board ("FASB") issued Accounting Standard Update ("ASU") No. 2016-02, *Leases (Topic 842)*, which supersedes the guidance in former ASC 840, Leases. The FASB issued further updates to this guidance in July 2018 through ASU 2018-10, 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 is effective for interim and annual periods beginning after December 15, 2018, with early adoption permitted, and is required to be adopted using a modified retrospective approach.

The Company is substantially complete with its evaluation of the effect that the adoption of this ASU will have on its consolidated financial statements. The Company plans to adopt this standard on January 1, 2019 applying the optional transition method such that it is not required to adjust prior period presentations. ASU 2016-02 is expected to impact the Company's consolidated financial statements as the Company has certain operating lease arrangements for which the Company is the lessee and one future operating lease arrangement for which the Company is the lessor. The Company has no financing leases. Management plans to elect 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 estimated impact of adoption of the standard is that the Company will recognize a net right of use asset and incremental lease liabilities of approximately $46.1 million, as of January 1, 2019. Management still does not expect the adoption to have a material change to the consolidated statements of operations and comprehensive loss, stockholders' equity (deficit), or cash flows.

Recently Adopted Accounting Pronouncements

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

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

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

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

In November 2018, the FASB issued ASU No. 2018-18, *Collaborative Arrangements (Topic 808): Clarifying the Interaction between Topic 808 and Topic 606*, which clarifies that certain transactions between collaborative arrangement participants should be accounted for as revenue under Topic 606 when the collaborative arrangement participant is a customer in the context of a unit of account. In those situations, all the guidance in Topic 606 should be applied, including recognition, measurement, presentation, and disclosure requirements. The standard adds unit-of-account guidance in Topic 808 to align with the guidance in Topic 606 (that is, a distinct good or service) when an entity is assessing whether the collaborative arrangement or a part of the arrangement is within the scope of Topic 606, and requires that in a transaction with a collaborative arrangement participant that is not directly related to sales to third parties, presenting the transaction together with customer revenue recognized under Topic 606 is precluded if the collaborative arrangement participant is not a customer. The standard is effective for interim and annual periods beginning after December 15, 2019, with early adoption permitted, including adoption in any interim period for public business entities for periods in which financial statements have not been issued. Amendments in the standard should be applied retrospectively to the date of initial application of Topic 606, but entities may elect to apply the amendments retrospectively either to all contracts or only to contracts that are not completed at the date of initial application of Topic 606, and should disclose the election. An entity may also elect to apply the practical expedient for contract modifications that is permitted for entities using the modified retrospective transition method in Topic 606. The Company has early adopted this standard as of December 31, 2018 and applied the standard retrospectively to January 1, 2018, the date of initial application of Topic 606. The new standard has been applied to all contracts, and there was no impact to the consolidated financial statements upon adoption.

2. Fair Value Measurements

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

	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

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

The carrying amounts of accounts receivable, 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, 2018 or 2017.

3. Cash and Marketable Securities

Cash, cash equivalents and restricted cash

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

	December 31, 2018	December 31, 2017	December 31, 2016
Cash and cash equivalents	$ 77,123	$ 218,375	$ 39,853
Restricted cash included within prepaid expenses and other current assets	—	84	—
Restricted cash included within other non-current assets	1,500	451	535
Total cash, cash equivalents, and restricted cash	$ 78,623	$ 218,910	$ 40,388

Marketable Securities

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

	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

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

As of December 31, 2018 and 2017, some of the Company's marketable securities were in an unrealized loss position. At each balance sheet date, the Company determined that it did have the ability and intent to hold all marketable securities that have been in a continuous loss position until maturity or recovery, thus there has been no recognition of any other-than-temporary impairment in the years ended December 31, 2018, 2017 or 2016. All marketable securities with unrealized losses as of each balance sheet date have been in a loss position for less than twelve months or the loss is not material.

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

4. Derivative Financial Instruments

Foreign Currency Exchange Rate Exposure

The Company uses forward foreign currency exchange contracts to hedge exposure to potential changes in foreign currency exchange rates. Such exposures result from certain external research and development activities taking place in foreign countries for which forecasted cash flows are 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, 2018 (notional amounts in thousands):

Foreign Exchange Contracts	Number of Contracts	Aggregate Notional[(1)] Amount in Foreign Currency	Maturity
Euros	23	2,343	Jan. 2019 - Nov. 2019
British Pounds	25	4,017	Jan. 2019 - Nov. 2019
Swiss Francs	20	1,100	Jan. 2019 - Nov. 2019
Total	68		

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

The derivative liability balance of $0.2 million is recorded in Other current liabilities and the derivative asset balance of $13,669 is recorded in Prepaid assets and other current assets on the consolidated balance sheet as of December 31, 2018. The Company recognized a net loss on forward foreign currency exchange contracts of $0.2 million in Interest and other income, net in the consolidated statement of operations and comprehensive loss for the year ended December 31, 2018.

5. Acquisition

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

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

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

The Company concluded that the assets acquired and liabilities assumed upon the exercise of the Option Agreement did not meet the accounting definition of a business, and as such, the acquisition was accounted for as an asset purchase. The Company recorded the upfront purchase price less estimated net liabilities acquired of $17.8 million in research and development expense in the accompanying consolidated statement of operations and comprehensive loss in the year ended December 31, 2018 since it represented consideration for in-process research and development with no future alternative use. The upfront option fee of $0.5 million previously included within other non-current assets was also included in research and development expense during the year ended December 31, 2018.

This transaction was accounted for as an asset purchase rather than a business combination, and the Company did not recognize any contingent consideration on the acquisition date. Contingent consideration is expected to be recognized in research and development expense in the future as incurred.

The Company was and continues to be responsible for certain research costs incurred by F-star Ltd in conducting activities under each agreed development plan, for up to 24 months. The research costs for the agreed TfR development plan was $2.1 million. The Company recognized $0.7 million, $1.1 million, and $0.3 million of research and development expense related to the funding of F-star Ltd activities under the TfR development plan during the years ended December 31, 2018, 2017, and 2016, 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 upon which 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 $600.0 million in clinical and regulatory milestone payments for CNS Products and $495.0 million in clinical, regulatory and commercial milestone payments for Peripheral Products, as defined.

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 Denali compared to RIPK1 Inhibitors contributed by Denali.

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 for Alzheimer’s disease and any activities required to support such clinical trials and specific for Alzheimer’s disease. Denali will also conduct, at Sanofi’s cost, a Phase 1b trial for the lead CNS penetrant RIPK1 inhibitor, 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. The Company will 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. The Company 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.

The Company 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 and country basis. Sanofi may also terminate Denali's cost-profit sharing provisions of the Sanofi Collaboration Agreement in its entirety if, following notice from Sanofi and a cure period, the Company fails to satisfy its cost-sharing obligations. After such an opt out by the Company or termination by Sanofi, Denali will no longer be obligated to share in the development and commercialization costs for the applicable CNS Products and Denali will not share in the applicable profits from such CNS Products. Instead, the Company will be entitled to receive tiered royalties on net sales of the applicable CNS Products in the relevant country (or countries). The royalty rates are 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 the Company has met certain co-funding thresholds at the time of its election or Sanofi’s termination of the Company's 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. 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 is probable that a significant reversal in the amount recognized will not occur. The transaction price increased by $2.3 million from inception through December 31, 2018 as payments for costs incurred related to the Retained Activities and associated activities were no longer constrained.

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.

A contract liability of $3.9 million is recorded on the balance sheet at December 31, 2018, which relates 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 is a receivable of $2.3 million as of December 31, 2018 associated with the Sanofi Collaboration Agreement.

In assessing the Sanofi Collaboration Agreement, management was required to exercise considerable judgment in estimating revenue to be recognized. Management applied 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, 2018, Denali has not achieved any milestones or 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 in respect of programs to develop and commercialize, jointly with the Company, certain biologic products that are enabled by three Denali's blood brain barrier ("BBB") delivery technology and intended for the treatment of neurodegenerative disorders. The programs were Denali's ATV:BACE1/Tau and ATV: TREM2 programs, as well as a third identified discovery stage program. 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, the agreement was amended to replace ATV:BACE1/Tau with ATV:Tau. 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.

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

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

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

In addition, Takeda may be obligated to pay Denali up to an aggregate of $707.5 million upon achievement of certain clinical and regulatory milestone events if Takeda exercises its option for all three collaboration programs. Takeda may also be obligated to pay Denali up to $75.0 million per biologic product upon achievement of a certain sales-based milestone, or an aggregate of $225.0 million if one biologic product from each program achieves 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. However, for each collaboration program, the Company may elect not to continue sharing development and commercialization costs, or Takeda may elect to terminate Denali's cost-profit sharing rights and obligations if, following notice from Takeda and a cure period, the Company fails to satisfy its cost sharing obligations with respect to the relevant collaboration program. After such an election by the Company or termination by Takeda becomes effective, Denali will no longer be obligated to share in the development and commercialization costs for the relevant collaboration program, and will not share in any profits from that collaboration program. Instead the Company will be entitled to receive tiered royalties. The royalties will be in the low- to mid-teen percentages on net sales, or low- to high-teen percentages on net sales if certain co-funding thresholds have been met at the time of the Company's election to opt out of co-development or Takeda's termination of Denali's cost-profit sharing rights and obligations, and, in each case, these royalty rates will be subject to certain reductions specified in the Takeda Collaboration Agreement. Takeda will pay these royalties for each biologic product included in the relevant collaboration program, on a country-by-country basis, until the latest of (i) the expiration of certain patents covering the relevant biologic product, (ii) the expiration of all regulatory exclusivity for that biologic product, and (iii) an agreed period of time after the first commercial sale of that biologic product in the applicable country, unless biosimilar competition in excess of a significant level specified in the Takeda Collaboration Agreement occurs earlier, in which case Takeda's royalty obligations in the applicable country would terminate.

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

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

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 sheet.

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

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

The Company has determined that all other goods or services which are contingent upon Takeda exercising its option for each program are not considered performance obligations at the inception of the 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. In October 2018, the Company confirmed the first preclinical milestone was met for the second program, triggering a milestone payment of $5.0 million, which was received in November 2018. In December 2018, the Company confirmed the first preclinical milestone was met for the third program, triggering a milestone payment of $5.0 million, which is recorded within Prepaid expenses and other current assets on the consolidated balance sheet at December 31, 2018. The payment was received in February 2019.

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 each program. There was no change in the transaction price from inception through December 31, 2018. This will be reassessed at each reporting period.

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

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

A contract liability of $64.9 million is recorded on the balance sheet at December 31, 2018, which relates 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.

Revenue recognized relating to future milestone payments of approximately $1.7 million, for which the Company concluded that it is probable that a significant reversal in the amount recognized will not occur, is presented net in the contract liability on the consolidated balance sheet.

Significant changes in the net contract liability balance during the year ended December 31, 2018 are as follows (in thousands):

	Contract liability
Balance at January 1, 2018	$ —
Increases due to cash received, excluding amounts recognized as revenue during the period	66,619
Decreases due to revenue recognized in the period for which cash has not been received	(1,701)
Balance at December 31, 2018	$ 64,918

There is a receivable of $5.0 million as of December 31, 2018 associated with the Takeda Collaboration Agreement.

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

Through December 31, 2018, Denali has recognized $15.0 million in milestones from Takeda and has not recorded any product sales under the Takeda Collaboration Agreement.

Collaboration Revenue

Revenue disaggregated by collaboration agreement and performance obligation for the year ended December 31, 2018 is as follows (in thousands):

	Revenue
Takeda Collaboration Agreement	$ 5,677
Sanofi Collaboration Agreement:	
CNS program license	73,932
Peripheral program license	47,148
Alzheimer's Disease Services	60
Retained Activities	2,343
Total Sanofi Collaboration Revenue	123,483
Total Collaboration Revenue	$ 129,160

There was no collaboration revenue in the years ended December 31, 2017 and 2016.

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 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 is obligated to use commercially reasonable efforts during the first three years of the agreement to research, develop and commercialize at least one licensed product.

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

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

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

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

The first clinical milestone of $2.5 million became due in June 2017 upon first patient dosing in the Phase 1 clinical trial for DNL201. The full amount was recorded as research and development expense in the year ended December 31, 2017.

8. Balance Sheet Components

Property and Equipment, Net

	December 31,	
	2018	2017
	(in thousands)	
Lab equipment	$ 14,352	$ 11,351
Leasehold improvements	22,288	7,737
Computers equipment and purchased software	458	439
Furniture and fixtures	74	65
	37,172	19,592
Less: accumulated depreciation	(12,010)	(4,669)
Total property and equipment, net	$ 25,162	$ 14,923

Depreciation expense was $7.4 million, $3.1 million and $1.5 million for the years ended December 31, 2018, 2017 and 2016, respectively.

Prepaid Expenses and Other Current Assets

	December 31,	
	2018	2017
	(in thousands)	
Prepaid research and development expenses	$ 6,643	$ 946
Collaboration accounts receivable	7,364	—
Prepaid insurance	—	927
Accrued interest on short-term marketable securities	1,182	464
Other prepaid and current assets	1,350	1,044
Total prepaid expenses and other current assets	$ 16,539	$ 3,381

Other Non-Current Assets

	December 31,	
	2018	2017
	(in thousands)	
Prepaid research and development expenses	$ 5,841	$ —
Other investments	—	500
Restricted cash	1,500	451
Other prepaid and non-current assets	764	490
Total other non-current assets	$ 8,105	$ 1,441

9. Commitments and Contingencies

Lease Obligations

In September 2015, the Company entered into a non-cancelable operating lease for its former corporate headquarters comprising 38,109 of rentable square feet in a building in South San Francisco (“Former Headquarters Lease”). The Former Headquarters Lease commenced on August 1, 2016 with a lease term of eight years. The Former Headquarters Lease provided for monthly base rent amounts escalating over the term of the lease. In addition, the Former Headquarters Lease provided both a tenant improvement allowance (“TIA”) of up to $7.4 million, of which $1.9 million would be repaid to the landlord in the form of additional monthly rent with interest applied.

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

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

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

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

The portion of the TIA utilized under the Headquarters Lease Amendment was $14.6 million, which is recorded as leasehold improvements and deferred rent liability on the consolidated balance sheet as of December 31, 2018. The Company will amortize the deferred rent liability as a reduction of rent expense and the leasehold improvement as depreciation expense of leasehold improvements ratably over the period of expected use, which is expected to commence in April 2019.

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, which is the legal commencement date of the Headquarters Lease Amendment, and provides for the Company to receive monthly base rent amounts escalating over the term of the lease, totaling approximately $14.8 million over the term of the Sublease Agreement.

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

As of December 31, 2018, the future minimum lease payments under all non-cancellable operating leases are as follows (in thousands):

Year Ending December 31:		
2019	$	4,941
2020		9,097
2021		9,716
2022		10,056
2023		10,408
2024 and later		60,882
	$	105,100

Rent expense for the years ended December 31, 2018, 2017 and 2016 was $6.0 million, $2.2 million, $1.0 million, respectively.

Indemnification

In the ordinary course of business, the Company may provide indemnifications of varying scope and terms to vendors, lessors, business partners, board members, officers, and other parties with respect to certain matters, including, but not limited to, losses arising out of breach of such agreements, services to be provided by the Company, negligence or willful misconduct of the Company, violations of law by the Company, or from intellectual property infringement claims made by third parties. In addition, the Company has entered into indemnification agreements with directors and certain officers and employees that will require the Company, among other things, to indemnify them against certain liabilities that may arise by reason of their status or service as directors, officers or employees. No demands have been made upon the Company to provide indemnification under such agreements, and thus, there are no claims that the Company is aware of that could have a material effect on the Company's 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 Lonza agreement will expire on September 6, 2022.

As of December 31, 2018 and 2017, the Company had non-cancellable purchase orders for biological product development and manufacturing costs totaling $24.7 million and $0.7 million, respectively. The activities under these purchase orders are expected to be completed by November 2024. During the year ended December 31, 2018, the Company incurred costs of $3.9 million and made payments of $3.4 million for the development and manufacturing services rendered under the agreement. The Company had not incurred any costs or made any payments for the manufacturing services rendered under the agreement for the year ended December 31, 2017. As of December 31, 2018 and 2017, the Company had total non-cancellable purchase commitments of $14.0 million and $0.4 million, respectively, under the DMSA.

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 $1.2 million and $1.6 million as of December 31, 2018 and 2017, 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, 2018 and 2017, 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 6,379,238 common shares for the issuance of stock options, restricted stock and other stock awards, to employees, non-employee directors, and consultants under terms and provisions established by the Board of Directors and approved by the stockholders. Awards granted under the 2017 Plan expire no later than ten years from the date of grant. For stock options, the option price shall not be less than 100% of the estimated fair value 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 8,325,000 common shares for the issuance of stock options, restricted stock and other stock awards, to employees, non-employee directors, and consultants under terms and provisions established by the Board of Directors and approved by the stockholders. Awards granted under the 2015 Plan expire no later than ten years from the date of grant. For stock options, the option price shall not be less than 100% of the estimated fair value of the Company's common stock on the day of grant. For all stock options granted between August 2015 and February 2016 with an exercise price of $0.68, a deemed fair value of $1.20 per share was used in calculating stock-based compensation expense, which was determined using management hindsight. Options granted typically vest over a four-year period but may be granted with different vesting terms.

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

As of December 31, 2018 and 2017, there were 2,289,196 and 6,012,498 common shares available for the Company to grant under the 2017 Plan. As of December 31, 2016, there were 1,813,321 shares available for the Company to grant under the 2015 Plan.

Stock Option Activity

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

	Number of Options	Weighted-Average Exercise Price	Weighted-Average remaining contractual life (years)	Aggregate Intrinsic Value (in thousands)
Balance at December 31, 2016	5,374,014	$ 1.77	9.03	$ 18,873
Options granted	2,183,365	8.78		
Options exercised	(695,192)	1.41		
Options forfeited	(172,708)	2.21		
Balance at December 31, 2017	6,689,479	$ 4.08	8.37	$ 77,317
Options granted	3,949,778	20.25		
Options exercised	(650,471)	2.78		
Options forfeited	(376,134)	12.48		
Balance at December 31, 2018	9,612,652	$ 10.49	8.20	$ 97,804
Options vested and expected to vest at December 31, 2018	7,867,920	$ 12.66	8.54	$ 62,944
Options exercisable at December 31, 2018	1,933,527	$ 4.50	7.64	$ 31,248

Aggregate intrinsic value represents the difference between the Company's estimated fair value of its common stock and the exercise price of outstanding options. The total intrinsic value of options exercised was $9.8 million, $3.5 million and $0.7 million for the years ended December 31, 2018, 2017 and 2016, respectively. During the years ended December 31, 2018, 2017, and 2016 the weighted-average grant-date fair value of the options vested was $3.85, $1.94, and $1.36 per share, respectively. The weighted-average grant date fair value of options granted during the years ended December 31, 2018, 2017 and 2016 was $14.79, $6.41, and $2.83 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,		
	2018	2017	2016
Expected term (in years)	5.50 - 6.08	6.08	6.00 - 6.08
Volatility	79.4% - 87.4%	81.9% - 91.3%	91.2% - 92.2%
Risk-free interest rate	2.6% - 3.1%	1.8% - 2.3%	1.2% - 2.1%
Dividend yield	—	—	—

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

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

Early Exercise of Stock Options

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

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

Performance Contingent Stock Options Granted to Employees

In August and November 2015, the Board of Directors granted 250,000 and 500,000 of stock option awards to certain executive officers, respectively. These awards have an exercise price of $0.68 per share.

These awards vest over time and include a performance provision which states that upon the occurrence of a change in control event, the vesting term would accelerate. Through December 31, 2018, the Company continues to believe that the achievement of the requisite performance condition is not probable and, as a result, the expense relating to these grants continues to be recognized over the initial time-based vesting period. If the performance goal is ever deemed to be probable of achievement, the recognition of compensation expense will be accelerated in accordance with the accelerated vesting schedule.

The estimated fair value of employee performance-contingent options was estimated at the date of grant using a Black-Scholes option-pricing model using the same assumptions as the Stock Options Granted to Employees with Service-based Vesting Valuation Assumptions.

Performance and Market Contingent Stock Options Granted to Employees

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

These awards have two separate market triggers for vesting based upon either (i) the successful achievement of stepped target closing prices on a national securities exchange for 90 consecutive trading days later than 180 days after the Company's initial public offering for its common stock, or (ii) stepped target prices for a change in control transaction. By definition, the market condition in these awards can only be achieved after the performance condition of a liquidity event has been achieved. As such, the requisite service period is based on the estimated period over which the market condition can be achieved. When a performance goal is deemed to be probable of achievement, time-based vesting and recognition of stock-based compensation expense commences. In the event any the milestones are not achieved by the specified timelines, such vesting award will terminate and no longer be exercisable with respect to that portion of the shares. The maximum potential expense associated with the performance- and market- contingent awards is $6.2 million, $5.8 million and $0.4 million of general and administrative and research and development expense, respectively if all of the performance and market conditions are achieved as stated in the option agreement. Through December 31, 2018, the Company continues to believe that the achievement of the requisite performance conditions is not probable and, as a result, no compensation cost has been recognized for these awards.

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

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

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

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

	Year Ended December 31,		
	2018	**2017**	**2016**
Expected term (in years)	7.14 - 9.86	7.50 - 8.09	8.50 - 9.70
Volatility	88.9% - 103.1%	86.1% - 88.1%	95.3% - 98.2%
Risk-free interest rate	2.7% - 3.0%	2.3% - 2.4%	2.4%
Dividend yield	—	—	—

Restricted Stock Activity

Under the 2017 Plan, the Company may grant restricted stock awards ("RSAs"), which represent restricted shares of common stock issued upon the date of grant in which the recipient's rights in the stock are restricted until the shares are vested, and restricted stock units ("RSUs"), which represent a commitment to issue shares of common stock in the future upon vesting. The fair value of restricted stock underlying the RSAs and RSUs is determined based on the closing 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 years ended December 31, 2018 and 2017 is summarized below:

	Share Awards & Units	Weighted-Average Fair Value at Date of Grant per Share
Unvested at December 31, 2016	3,922,638	$ 0.18
Granted	—	—
Vested	(1,628,850)	0.18
Forfeited	—	—
Unvested at December 31, 2017	2,293,788	$ 0.18
Granted	149,658	15.92
Vested	(1,940,203)	0.18
Forfeited	—	—
Unvested at December 31, 2018	503,243	$ 4.86
Vested and expected to vest – December 31, 2018	503,243	$ 4.86

There was $2.0 million and $0.3 million of total unrecognized stock-based compensation related to unvested RSAs and RSUs at December 31, 2018 and 2017 respectively, all of which is expected to be recognized over a remaining weighted-average period of 0.6 years and 1.0 year, respectively.

Employee Stock Purchase Plan

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

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

	Year Ended December 31,	
	2018	2017
Expected term (in years)	0.50 - 1.00	0.48 - 0.98
Volatility	61.0% - 64.3%	50.0% - 51.3%
Risk-free interest rate	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,		
	2018	2017	2016
Research and development	$ 10,093	$ 2,852	$ 2,078
General and administrative	8,698	1,557	873
Total	$ 18,791	$ 4,409	$ 2,951

As of December 31, 2018, total unamortized stock-based compensation expense related to unvested employee and non-employee awards that are expected to vest was $57.6 million. The weighted-average period over which such stock-based compensation expense will be recognized is approximately 3.0 years.

The Company recorded stock-based compensation expense for options issued to non-employees of $0.7 million, $0.7 million, and $1.0 million for the years ended December 31, 2018, 2017 and 2016, respectively.

12. Defined Contribution Plan

In January 2017, the Company began to sponsor 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 $0.9 million and $0.5 million for the years ended December 31, 2018 and 2017, respectively.

13. Income Taxes

The Company has reported pre-tax operating losses for all the 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, 2018, 2017, and 2016 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,		
	2018	2017	2016
Taxes at the U.S. statutory tax rate	21.0 %	34.0 %	34.0 %
Effect of Tax Act	—	(26.6)	—
Change in valuation allowance	(20.7)	(7.3)	(32.0)
Contingent consideration issued in tax-free reorganization	—	—	(2.1)
Research tax credits	10.2	1.0	0.6
Stock-based compensation	(0.7)	(1.0)	(0.5)
Nondeductible acquisition-related costs	(9.5)	—	—
Other	(0.3)	(0.1)	—
Total provision for income taxes	—%	—%	— %

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

	December 31,	
	2018	2017
Deferred tax assets:		
Net operating loss carryforwards	$ 35,023	$ 37,606
Tax credit carryforwards	9,565	4,072
Reserves and accruals	7,309	3,328
Capitalized start-up costs	4,464	6,248
Intangibles	5,401	5,300
Share based compensation	3,305	733
Other	7	7
Gross deferred tax assets	65,074	57,294
Valuation allowance	(60,915)	(54,650)
Net deferred tax assets	4,159	2,644
Deferred tax liabilities:		
Property and equipment	(4,159)	(2,618)
Stock-based compensation	—	(26)
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, 2018 and 2017.

On December 22, 2017, the U.S. government enacted the Tax Act. The Act reduced the corporate tax rate to 21 percent, effective January 1, 2018. The tax rate decrease resulted in a reduction of $6.3 million in the Company's deferred tax assets as of December 31, 2017, and a corresponding decrease of the same amount in the valuation allowance, as substantially all of the Company's deferred tax assets, net of deferred tax liabilities, are subject to a full valuation allowance.

As of December 31, 2018, the Company has federal net operating loss ("NOL") carryforwards of approximately $118.6 million, which are available to reduce future taxable income, and has federal tax credits of approximately $7.5 million which may be used to offset future tax liabilities. The federal NOL and federal tax credit carryforwards will begin to expire in 2035. The Company also has state NOL carryforwards of approximately $134.0 million, which are available to reduce future taxable income, and has state tax credits of approximately $5.7 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,		
	2018	2017	2016
Unrecognized tax benefits at January 1	$ 1,146	$ 531	$ 122
Additions for tax positions taken in a prior year	—	—	7
Additions for tax positions taken in the current year	1,506	640	411
Reductions for tax positions taken in the prior year	(10)	(25)	(9)
Unrecognized tax benefits at December 31	$ 2,642	$ 1,146	$ 531

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, 2018, 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

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

	Year Ended December 31,		
	2018	2017	2016
Numerator:			
Net loss	$ (36,240)	$ (88,185)	$ (86,652)
Denominator:			
Weighted average common shares outstanding	92,621,991	14,964,144	6,424,720
Net loss per share, basic and diluted	$ (0.39)	$ (5.89)	$ (13.49)

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,		
	2018	2017	2016
Series A-1 convertible preferred stock	—	—	46,114,423
Series A-2 convertible preferred stock	—	—	4,361,527
Series B-1 convertible preferred stock	—	—	8,124,365
Options issued and outstanding and ESPP shares issuable and outstanding	9,789,594	6,835,313	5,374,014
Restricted shares subject to future vesting	503,243	2,293,788	3,922,638
Early exercised common stock subject to future vesting	135,424	369,796	510,417
Shares to be issued under Incro acquisition agreement	—	—	81,164
Total	10,428,261	9,498,897	68,488,548

15. Selected Quarterly Financial Data (Unaudited)

The following table provides the selected quarterly financial data for the years ended December 31, 2018 and 2017 (in thousands, except per share amounts):

	Quarter Ended			
	December 31, 2018	September 30, 2018	June 30, 2018	March 31, 2018
Collaboration revenue	$ 125,676	$ 1,195	$ 1,648	$ 641
Profit (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	$ 0.82	$ (0.38)	$ (0.59)	$ (0.26)
Net income (loss) per share, diluted[(1)]	$ 0.79	$ (0.38)	$ (0.59)	$ (0.26)

[(1)] Diluted net income per share for the quarter ended December 31, 2018 is calculated using 97,746,224 shares, which is computed by giving effect to all dilutive potential ordinary shares including options.

	Quarter Ended			
	December 31, 2017	September 30, 2017	June 30, 2017	March 31, 2017
Loss from operations	$ (23,540)	$ (22,288)	$ (22,568)	$ (21,744)
Net loss	(22,887)	(21,844)	(22,134)	(21,320)
Net loss per share, basic and diluted	$ (0.74)	$ (2.14)	$ (2.29)	$ (2.36)

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

Any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objective and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on this evaluation, our Chief Executive Officer and Chief Financial Officer concluded that, as of December 31, 2018, the design and operation of our disclosure controls and procedures were effective at a reasonable assurance level.

Changes in Internal Control over Financial Reporting

There was no change in our internal control over financial reporting identified in connection with the evaluation required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the quarter ended December 31, 2018 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Management's 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, 2018 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, 2018.

This Annual Report on Form 10-K does not include an attestation report of our independent registered public accounting firm on our internal control over financial reporting due to an exemption established by the JOBS Act for "emerging growth companies."

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 2019 Annual Meeting of Stockholders (the “Proxy Statement”), which is expected to be filed not later than 120 days after December 31, 2018, 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
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	10.16	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 Corporate ("Sanofi"), dated October 29, 2018	—	—	—	Filed herewith
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, 2018, formatted in XBRL (eXtensible Business Reporting Language): (i) Consolidated Balance Sheets, (ii) Consolidated Statements of Operations and Comprehensive Loss, (iii) Consolidated Statements of Cash Flows and (iv) Notes to Consolidated Financial Statements.	—	—	—	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: March 12, 2019

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)*	March 12, 2019
/s/ Steve E. Krognes Steve E. Krognes	Chief Financial Officer and Treasurer *(Principal Financial and Accounting Officer)*	March 12, 2019
/s/ Vicki Sato Vicki Sato, Ph.D.	Chairperson of our Board of Directors	March 12, 2019
/s/ Marc Tessier-Lavigne Marc Tessier-Lavigne, Ph.D.	Director	March 12, 2019
/s/ Douglas Cole Douglas Cole, M.D.	Director	March 12, 2019
/s/ Jennifer Cook Jennifer Cook	Director	March 12, 2019
/s/ Jay Flatley Jay Flatley	Director	March 12, 2019
/s/ Peter Klein Peter Klein	Director	March 12, 2019
/s/ Robert Nelsen Robert Nelsen	Director	March 12, 2019
/s/ David Schenkein David Schenkein, M.D.	Director	March 12, 2019

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

COLLABORATION AND LICENSE AGREEMENT

between

DENALI THERAPEUTICS INC.

and

GENZYME CORPORATION

October 29, 2018

Confidential

COLLABORATION AND LICENSE AGREEMENT

This Collaboration and License Agreement ("**Agreement**") is made and entered into effective as of October 29, 2018 ("**Execution Date**") by and between Denali Therapeutics Inc., a Delaware corporation ("**Denali**") with its principal place of business located at 151 Oyster Point Blvd., South San Francisco, California 94080, U.S.A., and Genzyme Corporation, a Massachusetts corporation ("**Sanofi**") with its principal place of business located at 50 Binney Street, Cambridge, Massachusetts 02142. Denali and Sanofi are sometimes referred to herein individually as a "**Party**" and collectively as the "**Parties**."

RECITALS

WHEREAS, Denali has developed certain Licensed Compounds and Licensed Products (each, as defined herein) that are RIPK1 Inhibitors (as defined herein) and controls certain intellectual property and other rights with respect to such Licensed Compounds and Licensed Products in the Territory (as defined herein);

WHEREAS, Denali wishes to grant to Sanofi a license under Denali's intellectual property with respect to Licensed Compounds and Licensed Products, and Sanofi wishes to obtain such license, for purposes of Developing, Manufacturing and Commercializing Licensed Compounds and Licensed Products in the Territory, each in accordance with the terms and conditions set forth below; and

WHEREAS, the Parties wish to collaborate in the Development and Commercialization of CNS Compounds and CNS Products and desire that Sanofi conduct Development and Commercialization of Peripheral Compounds and Peripheral Products, in each case in accordance with the terms and conditions set forth below.

NOW, THEREFORE, in consideration of the premises and the mutual promises and conditions hereinafter set forth, and other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties, intending to be legally bound, do hereby agree as follows:

ARTICLE 1
DEFINITIONS

Unless otherwise specifically provided herein, the following terms shall have the following meanings:

1.1 "**Accounting Standards**" means, with respect to a Party and its Affiliates, the United States Generally Accepted Accounting Principles or International Financial Reporting Standards, as such Party uses for its financial reporting obligations, consistently applied.

1.2 "**Active Comparator Costs**" means the Out-of-Pocket Costs to acquire active comparators from Third Parties or of the Manufacturing Costs for any active comparators that are a product of Sanofi or any of its Affiliates.

1.3 "**Acquisition**" means, with respect to a Party, an acquisition by such Party of a Third Party (whether by merger or acquisition of all or substantially all of the stock or of all or substantially all of the assets of a Third Party or of any operating or business division of a Third Party or similar transaction), other than a Change in Control of the Party.

1.4 "**Additional CNS Development Costs**" means those Development Costs incurred by the Proposing Party in performing the relevant Additional CNS Development Activities, which Development Costs shall be determined using the same manner of calculating Shared Development Costs and Allowable Expenses as if such Additional CNS Development Activities had been incorporated into the CNS Development Plan.

1.5 "**Affiliate**" means, with respect to a Person, any other Person that, directly or indirectly, through one (1) or more intermediaries, controls, is controlled by or is under common control with such Person. For purposes of this definition, "control" and, with correlative meanings, the terms "controlled by" and "under common control with" means (a) the possession, directly or indirectly, of the power to direct the management or policies of a Person, whether through the ownership of voting securities, by contract relating to voting rights or corporate governance, or otherwise; or (b) the ownership, directly or indirectly, of more than fifty percent (50%) of the voting securities or other ownership interest of a Person (or, with respect to a limited partnership or other similar entity, its general partner or controlling entity). The Parties acknowledge that in the case of certain entities organized under the laws of certain countries outside of the United States, the maximum percentage ownership permitted by law for a foreign investor may be less than fifty percent (50%), and that, in such case, such lower percentage shall be substituted in the preceding sentence, *provided* that such foreign investor has the power to direct the management or policies of such entity.

1.6 "**Allowable Expenses**" means, on a Cost Profit Sharing Product-by-Cost Profit Sharing Product and Cost Profit Sharing Country-by-Cost Profit Sharing Country basis, all FTE Costs and Out-of-Pocket Costs incurred by, or on behalf of, a Party that are allocable to Cost Profit Sharing Products in the corresponding Cost Profit Sharing Country to the extent specifically identifiable or reasonably allocable to:

1.6.1 the Commercialization of Cost Profit Sharing Products in the Cost Profit Sharing Country including the following: sales, pricing, activities relating to obtaining and managing reimbursement from payers and reimbursement authorities, contracting (including account managers), launch timing, internal distribution-related activities with respect to finished CNS Product(s) (including custom duties, order handling, transportation and storage), which shall be invoiced as a percentage (%) of Net Sales ([***], as applicable), activities directed to advertising and marketing (including marketing messaging, product positioning, development and distribution of selling, advertising and promotional materials), sales tracking and auditing, market research, marketing studies and product usage surveys, provision of medical affairs support staff and conduct of activities by such medical affairs support staff, and scientific and medical advisory boards (including any global medical conferences and other seminars and conventions), medical liaisons and health outcome liaisons, peer-to-peer activities and speaker

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programs; in each case, with respect to Cost Profit Sharing Products in the Cost Profit Sharing Country;

1.6.2 the sales force costs for Cost Profit Sharing Products in the Cost Profit Sharing Country;

1.6.3 training, operation (including CRM platforms) and management (including on-board and off-boarding) of sales representatives and medical affairs support staff engaged in activities relating to the Co-Commercialization Activities in the Cost Profit Sharing Country;

1.6.4 activities pertaining to preparation for, and the conduct of, any marketing study, epidemiological study, modeling and pharmaco-economic study, registries, Phase IV Marketing Studies (including investigator sponsorship trials ("**ISTs**"), EAP (extended access programs), open label extensions or long term safety studies, health economic and outcome research or post-marketing surveillance studies (including post-approval safety studies and post-approval efficacy studies) of a Cost Profit Sharing Product in the Cost Profit Sharing Country described in **Section 1.29** ("Commercialization" definition) (in each case, to the extent such studies are not intended for use as a basis for obtaining Regulatory Approval in such country (including expanded labeling) with respect to the applicable Cost Profit Sharing Product in the Cost Profit Sharing Country);

1.6.5 the preparation of Regulatory Documentation as reasonably necessary to conduct Commercialization activities for Cost Profit Sharing Products in the Cost Profit Sharing Country, including to the extent applicable in such country, any Regulatory Documentation pertaining to pricing and reimbursement approvals for a Cost Profit Sharing Product in the Cost Profit Sharing Country and any filing fees incurred in connection therewith (excluding any fees associated with Regulatory Documentation that is the subject of Development Costs);

1.6.6 Indemnified Losses and other Out-of-Pocket Costs incurred in connection with Third Party Claims involving a Cost Profit Sharing Product in the Cost Profit Sharing Country to the extent (a) not subject to indemnification by either Party under this Agreement, and (b) specified in **Section 12.3** (Certain Indemnified Losses) to be treated as Allowable Expenses;

1.6.7 any recalls and withdrawals of a Cost Profit Sharing Product in such country to the extent (a) treated as an Allowable Expense pursuant to **Section 5.10** (Recalls, Market Withdrawals or Corrective Actions), and (b) not subject to indemnification by either Party under this Agreement;

1.6.8 payment made: (a) by a Party to a Third Party with respect to New CNS Program Technology for a Cost Profit Sharing Product in the Cost Profit Sharing Country in accordance with **Section 6.5.2** (New Technology), or (b) by Denali to a Third Party under an Existing License Agreement to the extent such payments will be shared by the Parties as Allowable Expenses in accordance with **Section 7.5.4(c)** (In-License Agreements);

1.6.9 the Manufacturing Costs (a) for any samples of Cost Profit Sharing Product in the Cost Profit Sharing Country, or (b) for any supply of Cost Profit Sharing Products in the Cost Profit Sharing Country intended for Commercial sale or for use in any Phase IV Marketing Study or epidemiological study, modeling and pharmaco-economic study, investigator-initiated clinical trial or post-marketing surveillance study or other clinical study described in **Section 1.6.4** or **Section 1.29** ("Commercialization" definition), in each case ((a) and (b));

1.6.10 the Manufacturing-related activities pertaining to Cost Profit Sharing Products in the Cost Profit Sharing Country not otherwise included in Manufacturing Costs, including stability testing and other CMC support costs with respect to Cost Profit Sharing Products in the Cost Profit Sharing Country, but only to the extent such costs are not included in Shared Development Costs; and

1.6.11 any other FTE Costs and Out-of-Pocket Costs incurred with respect to such Cost Profit Sharing Product in the Cost Profit Sharing Country and specified to be an Allowable Expense in this Agreement or otherwise mutually agreed in writing to be shared by the Parties as an Allowable Expense as set forth in this Agreement.

For clarity: (A) with respect to any of the FTE Costs or Out-of-Pocket Costs described in **Sections 1.6.1** through **1.6.5**, **1.6.9** and **1.6.10**, such FTE Costs or Out-of-Pocket Costs shall only be included in the calculation of Allowable Expenses to the extent they are incurred in accordance with the applicable Co-Commercialization Plan and Co-Commercialization Budget and, with respect to **Section 1.6.2**, shall be calculated in accordance with **Section 5.4.2** (Calculation of Sales Force Costs); (B) Allowable Expenses are exclusive of and do not include Development Costs or any expenses or costs to the extent allocable to Commercialization activities for (i) any CNS Product for any country that is not a Cost Profit Sharing Product in a Cost Profit Sharing Country, or (ii) the Peripheral Program anywhere in the Territory; and (C) Allowable Expenses shall not include any FTE Costs or Out-of-Pocket Costs with respect to any item described in **Section 1.6.1** through **Section 1.6.11** incurred for a Cost Profit Sharing Product in the Cost Profit Sharing Country after the Co-Funding End Date for such Cost Profit Sharing Product. Notwithstanding **Section 1.44** ("Development Costs" definition), **Section 1.85** ("Manufacturing Cost" definition) and **Section 1.90** ("Net Sales" definition) or otherwise in this Agreement, any costs or expenses included in Allowable Expenses shall not be, or have not been, deducted from the total amount billed or invoiced on sales of a Cost Profit Sharing Product in order to calculate Net Sales, nor included in the calculation of Manufacturing Costs or Development Costs, and in no event shall any cost or expense be counted more than once, *e.g.*, if a cost or expense is deducted in the calculation of Allowable Expenses then it will not be, or not have been, deducted in the calculation of Net Sales independently of the calculation of Allowable Expenses, including, for example, the fixed percentage deductions in **Section 1.6.1** for distribution-related activities and deductions for fees for distribution services under clause (b) of **Section 1.90.7** (in definition of Net Sales).

1.7 "**ALS**" or "**Amyotrophic Lateral Sclerosis**" means an Indication [***].

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1.8 "**Alzheimer's Disease**" means an Indication [***].

1.9 "**Annual CNS Net Sales**" means the total Net Sales of the applicable CNS Product in the Territory in a given Calendar Year, *provided* that if such CNS Product is a Cost Profit Sharing Product, then Net Sales of such CNS Product in the applicable Cost Profit Sharing Country(ies) in a given Calendar Year shall be excluded.

1.10 "**Annual Worldwide Peripheral Net Sales**" means the total Net Sales of the applicable Peripheral Product in the Territory in a given Calendar Year.

1.11 "**Applicable Law**" means federal, state, local, national and supra-national laws, statutes, rules and regulations, including any rules, regulations, regulatory guidelines or other requirements of the Regulatory Authorities, major national securities exchanges or major securities listing organizations, that may be in effect from time to time during the Term and applicable to a particular activity or country or other jurisdiction hereunder.

1.12 "**Business Day**" means a day, other than a Saturday or Sunday, on which banking institutions in San Francisco, California, U.S.A., and in Paris, France, are open for business.

1.13 "**Calendar Quarter**" means each successive period of three (3) calendar months commencing on January 1, April 1, July 1 and October 1, except that the first Calendar Quarter shall commence on the Effective Date and end on the day immediately prior to the first to occur of January 1, April 1, July 1 or October 1 after the Effective Date, and the last Calendar Quarter shall end on the last day of the Term.

1.14 "**Calendar Year**" means each successive period of twelve (12) calendar months commencing on January 1 and ending on December 31, except that the first Calendar Year shall commence on the Effective Date and end on December 31 of the year in which the Effective Date occurs and the last Calendar Year of the Term shall commence on January 1 of the year in which the Term ends and end on the last day of the Term.

1.15 "**Centralized Approval Procedure**" means the procedure through which an MAA filed with the EMA results in a single marketing authorization valid throughout the European Union (or at least all Major Markets that are within the European Union or otherwise subject to such marketing authorization procedure, such as the United Kingdom if and as applicable).

1.16 "**Change in Control**," with respect to a Party, means any transaction or series of related transactions in which such Party: (a) sells, conveys or otherwise disposes of all or substantially all, whether directly or indirectly, of its assets or business; or (b)(i) merges, consolidates with, or is acquired by any other Person (other than an Affiliate of such Party, *provided* that such Person was an Affiliate of such Party prior to the Execution Date); or (ii) effects any other transaction or series of related transactions; in each case of subsection (i) or (ii), such that the stockholders of such Party immediately prior thereto, in the aggregate, no longer own, directly or indirectly, beneficially or legally, at least fifty percent (50%) of the outstanding voting securities, capital stock or other ownership interest of the surviving Person following the closing of such merger, consolidation, other transaction or series of related transactions. The Parties acknowledge that in

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the case of certain entities organized under the laws of certain countries outside of the United States, the maximum percentage ownership permitted by law for a foreign investor may be less than fifty percent (50%), and that, in such case, the effective inverse of such lower percentage shall be substituted in the preceding sentence (*e.g.*, if such maximum percentage ownership is thirty percent (30%), then seventy percent (70%) shall be substituted for fifty percent (50%) in the prior sentence), *provided* that such foreign investor has the power to direct the management or policies of such entity.

1.17 "**Clinical Data**" means the original source patient data and case report forms (CRFs) collected or generated by, on behalf of, or under the authority of a Party with respect to Clinical Studies of any Compound or Product, together with all analysis, reports, and results with respect thereto.

1.18 "**Clinical Studies**" means any Phase I Trial, Phase II Trial, Phase III Trial, Phase IV Development Study or Phase IV Marketing Study or any such other test or study in human subjects.

1.19 "**CNS Compound**" means a CNS Licensed Compound or a Sanofi CNS Compound.

1.20 "**CNS Development Plan**" means the plan for the Development of CNS Compounds and CNS Products (other than any Cost Profit Sharing Opt Out Product(s) in a Cost Profit Sharing Opt Out Country), including the CNS Development Budget, as described in the Initial CNS Development Plan as modified from time to time in accordance with the terms of this Agreement.

1.21 "**CNS Licensed Compound**" means: (a) each of the small molecule compounds known internally at Denali as "DNL747", [***]; and (b) any CNS Penetrant Compound that is a RIPK1 Inhibitor that (i) (A) has been [***], or (B) that is/was [***]; or (iii) [***]; but excluding, in each case, any [***].

1.22 "**CNS Licensed Product**" means any product containing, alone or in combination with one or more Other Active Ingredients, a CNS Licensed Compound, in any formulation, dosage strength or method of delivery.

1.23 "**CNS Penetrant Compound**" means, with respect to a compound, (a) [***] with respect to [***], and (b) with respect to [***]. Notwithstanding anything to the contrary in this Agreement, the small molecule compounds known as "DNL747", [***] each shall be deemed to be a CNS Penetrant Compound and a CNS Licensed Compound, and the small molecule compounds known as "DNL758", [***] each shall be deemed not to be a CNS Penetrant Compound and shall be deemed a Peripheral Licensed Compound.

1.24 "**CNS Product**" means a CNS Licensed Product or a Sanofi CNS Product.

1.25 "**CNS Program**" means all CNS Compounds and CNS Products, and the Development activities, Manufacturing activities and Commercialization activities with respect to such CNS Compounds and CNS Products.

1.26 "**Co-Commercialization Budget**" means a rolling [***] Calendar Year budget setting forth the total budgeted amounts estimated to be incurred in performance of Commercialization activities for each of the Cost Profit Sharing Products in the applicable Cost Profit Sharing Country(ies) included in the Co-Commercialization Plan pertaining to each applicable Cost Profit Sharing Product for the applicable Cost Profit Sharing Country(ies) in the first Calendar Year (or part thereof) of such budget and the overall estimated budget to be incurred in performance of Commercialization activities included in the Co-Commercialization Plan pertaining to all such Cost Profit Sharing Products for the applicable Cost Profit Sharing Country for the next [***] thereafter, including a reasonably detailed budget for FTE Costs and Out-of-Pocket Costs, broken down by Calendar Quarter for the first Calendar Year (or part thereof) and a then current estimate of such FTE Costs and Out-of-Pocket Costs for the next [***], and, as determined by the JCC (or if Denali is not conducting Co-Commercialization Activities by the JSC), a further breakout of costs by functional area or category. For the avoidance of doubt, the Co-Commercialization Budget shall include Cost Profit Sharing Product(s) for which Denali is not conducting Co-Commercialization Activities.

1.27 "**Co-Commercialization Plan**" means a plan for the Commercialization of applicable Cost Profit Sharing Products in a Cost Profit Sharing Country, as described in **Section 5.3.2** (Co-Commercialization Plan). For the avoidance of doubt, the Co-Commercialization Plan shall include Cost Profit Sharing Product(s) for which Denali is not conducting Co-Commercialization Activities.

1.28 "**Combination Product**" means a Product that includes one (1) or more Compounds as an active ingredient together with one (1) or more Other Active Ingredients, whether in the same or different formulations, so long as both the Compound(s) and Other Active Ingredient(s) are sold together as a single unit or for a single price.

1.29 "**Commercialization**" means any and all activities directed to the preparation for sale of, offering for sale of, or sale of a Product, including: marketing, promoting, distributing, medical affairs, obtaining pricing and reimbursement approval for a Product, and so called "treatment IND sales", "named patient sales" and "compassionate use sales," in each case to the extent sold above cost; any marketing study, epidemiological study, modeling and pharmaco-economic study, investigator-initiated clinical trial or post-marketing surveillance study of a Product, in each case that is not intended for use as a basis for obtaining Regulatory Approval (including expanded labeling) with respect to such Product; Manufacturing Products for commercial sale, samples or any of the foregoing studies; importing and exporting Products; and the preparation and submission of Regulatory Documentation and interacting with Regulatory Authorities regarding any of the foregoing activities. When used as a verb, "**Commercialize**" and "**Commercializing**" means to engage in Commercialization, and "**Commercialized**" has a corresponding meaning. When used as an adjective, "**Commercial**" modifies the following noun to allow for the foregoing activities.

1.30 "**Commercialization Plans**" means each Co-Commercialization Plan (including the Co-Commercialization Budget) and Global Commercialization Plan.

1.31 "**Commercially Reasonable Efforts**" means [***].

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

1.32 "**Competitively Sensitive Information**" means Confidential Information of a Party pertaining to [***].

1.33 "**Compound**" means a Peripheral Compound or a CNS Compound.

1.34 "**Confidential Information**" means any proprietary Information or data provided orally, visually, in writing or other form by or on behalf of one Party (or an Affiliate or representative of such Party or such Party's Affiliate) to the other Party (or to an Affiliate or representative of such Party or such Party's Affiliate) in connection with this Agreement, whether prior to, on, or after the Execution Date, including Information pertaining to the terms of this Agreement, a Compound or any Product (including relevant Regulatory Documentation and Regulatory Data), any Exploitation of a Compound or Product, any Information with respect thereto developed by or on behalf of the disclosing Party or its Affiliates (including Sanofi Know-How and Denali Know-How), or the scientific, regulatory or business affairs or other activities of either Party. Notwithstanding the foregoing, Joint Program Know-How and all Regulatory Documentation generated after the Execution Date and owned by a Party pursuant to this Agreement shall be deemed to be the Confidential Information of both Parties, and the restrictions on use and disclosure in **Section 10.1** (Confidentiality Obligations) and **Section 10.3** (Permitted Disclosures) shall be deemed to apply to each Party as a receiving Party, regardless of which Party initially generated or disclosed the relevant Joint Program Know-How or Regulatory Documentation, as applicable, to the other Party in connection with this Agreement.

1.35 "**Control**" or "**Controlled**" means, with respect to a Party or its Affiliate and any item of Information, Regulatory Documentation, material, Patent, or other intellectual property right, the ownership of such intellectual property right or the possession of a license (or sublicense) or right of access or use to the item of Information, Regulatory Documentation, material, Patent, or other intellectual property right by such Party or its Affiliate (other than by operation of the license and other grants in **Section 6.1** (License Grants to Sanofi) and **Section 6.2** (License Grants to Denali)), in each case with the ability to grant a license (or sublicense), or a right of access (including the Right of Reference) or use, under such item of Information, Regulatory Documentation, material, Patent, or other intellectual property right on the terms and conditions set forth in this Agreement, without violating the terms of any agreement or other arrangement with any Third Party.

1.36 "**Corporate Names**" means the Trademarks and logos identified on **Schedule 1.36** and such other names and logos, in each case as Denali or Sanofi may designate in writing from time to time.

1.37 "**Cover**," "**Covering**" or "**Covered**" means, with respect to a compound, product, or other composition of matter, or technology, process or method, that, in the absence of ownership of, or a license to, a Patent, the practice or Exploitation of such compound, product, or other composition of matter, or technology, process or method would infringe such Patent or, in the case of a Patent that has not yet issued, would infringe such Patent if it were to issue.

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1.38 "**Denali CNS Development Activities**" means: [***].

1.39 "**Denali Know-How**" means proprietary Information, including any related Regulatory Documentation and Clinical Data, Controlled by Denali or any of its Affiliates (a) as of the Effective Date or during the Term and that is reasonably necessary or reasonably useful for the Development, Manufacture, Commercialization or other Exploitation of Licensed Compounds or Licensed Products; or (b) generated by or on behalf of Denali or any of its Affiliates in the performance of activities with respect to the Development, Manufacture, Commercialization or other Exploitation of any Compound(s) or Product(s) under this Agreement during the Term or during any post-termination transition activities conducted pursuant to **Section 13.8** (Effects of Termination), including Denali's joint interest in any Joint Program Know-How.

1.40 "**Denali Patents**" means Patents Controlled by Denali or any of its Affiliates (a) issued or filed before, on or after the Effective Date and during the Term and that are reasonably necessary or reasonably useful for the Development, Manufacture, Commercialization or other Exploitation of Licensed Compounds or Licensed Products, including diagnostic tools or biomarkers pertaining thereto or (b) Covering inventions or discoveries conceived by or on behalf of Denali or any of its Affiliates in the performance of activities with respect to the Development, Manufacture, Commercialization or other Exploitation of any Compound(s) or Product(s) under this Agreement during the Term or during any post-termination transition activities conducted pursuant to **Section 13.8** (Effects of Termination). For clarity, Product Patents, Program Patents, and Joint Program Patents to the extent Controlled by Denali or any of its Affiliates and, in each case, that meet the foregoing requirements of clause (a) or (b) are Denali Patents.

1.41 "**Denali Technology**" means, collectively, the Denali Patents and the Denali Know-How.

1.42 "**Detail**" means a face-to-face meeting in an individual or group practice setting (or other method of individual contact if mutually agreed by the Parties), including a hospital setting, between a professional sales representative of the applicable Party, and a health care professional licensed or authorized to prescribe drugs, during which a presentation of a CNS Product's attributes is presented in a manner consistent with Applicable Law and industry standards and with the quality of similar presentations made by a Party's sales representatives for such Party's other products, if applicable. A Detail does not include a reminder or sample drop made by a sales representative or contacts made at conventions, exhibit booths or speaker meetings, to managed care representatives not specifically provided as part of the Co-Commercialization Operational Plan (as defined in **Schedule 5.2.4**). "**Detailing**" shall mean the act of presenting a Detail.

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1.43 "**Development**" means any and all activities related to research, pre-clinical and other non-clinical testing, and Clinical Studies, including test method development and stability testing, toxicology, formulation, process development, device development, Manufacturing in support of the foregoing activities and manufacturing scale-up, qualification and validation, quality assurance/quality control, any statistical analysis and report writing, the preparation and submission of Regulatory Documentation pertaining to seeking and obtaining Regulatory Approval for a therapeutic product (excluding any activities required solely for obtaining pricing and reimbursement approval but not for other elements of the Regulatory Approval) and interacting with Regulatory Authorities regarding any of the foregoing. When used as a verb, "**Develop**" means to engage in Development and "**Developed**" has a corresponding meaning.

1.44 "**Development Costs**" means all Out-of-Pocket Costs and FTE Costs incurred by or on behalf of a Party to the extent specifically identifiable or reasonably allocable to the activities conducted pursuant to this Agreement with respect to a Compound(s) or Product(s) and whether or not to be shared between the Parties. Subject to the foregoing, Development Costs shall include Out-of-Pocket Costs and FTE Costs attributable to the following Development activities conducted under this Agreement:

1.44.1 research, pre-clinical and non-clinical activities with respect to a Compound or Product, such as toxicology and formulation development, test method development, stability testing, quality assurance, quality control development and statistical analysis;

1.44.2 Clinical Studies (other than Phase IV Marketing Studies) for a Product, including (i) the preparation for and conduct of such Clinical Studies; (ii) data collection and analysis and report writing; (iii) clinical laboratory work; (iv) regulatory activities in direct connection with such studies, including adverse event recordation and reporting; and (v) advisory meetings in connection with such Compound or Product;

1.44.3 the preparation and submission of Regulatory Documentation as reasonably necessary to conduct Development activities with respect to a Compound or Product, including any Regulatory Documentation reasonably necessary to obtain or maintain any Regulatory Approval for a Product and, in all cases, any filing fees incurred in connection therewith, but excluding any Regulatory Documentation pertaining to pricing and reimbursement approvals and any filing fees associated therewith;

1.44.4 the Manufacturing Costs for any such Compound, Product, comparators or placebo reasonably necessary to conduct Development activities with respect to a Compound or Product under this Agreement;

1.44.5 the disposal of Compounds and Products and other supplies manufactured for, or used in, the conduct of Development activities with respect to a Compound or Product, including the disposal of Compounds and Products and other supplies that are manufacture failure or obsolescence according to the then-existing standards of the Manufacturing Party; and

1.44.6 the development of the manufacturing process for such a Compound or Product, manufacturing process validation, including validation batches, and qualification and validation of manufacturing Third Party Providers.

1.45 "**Development Lead**" means the Party specified as the "Development Lead" pursuant to the terms of **Section 3.2.3(d)** (Designation of Development Lead for the CNS Program).

1.46 "**Development Plans**" means the CNS Development Plan and Peripheral Development Plan.

1.47 "**Divestiture**" means: (a) the divestiture of a Competing Product through: (i) an outright sale or assignment of all material rights in such Competing Product to a Third Party; or (ii) an exclusive out-license of all Development and commercialization rights with respect to such Competing Product, in each case in the Field with no further material role, influence or authority of the applicable Party, directly or indirectly, with respect to such Competing Product in the Field; or (b) the complete cessation of all Development and commercialization activities with respect to such Competing Product in the Field. For clarity, the right of the applicable Party to receive royalties, milestones or other payments in connection with an acquirer, assignee or licensee's Development or commercialization of a Competing Product pursuant to sub-section (a) above, shall be permitted for any such Divestiture. When used as a verb, "**Divest**" and "**Divested**" means to cause a Divestiture.

1.48 "**Dollars**" or "**$**" means United States Dollars.

1.49 "**Drug Approval Application**" means a New Drug Application as defined in the FFDCA ("**NDA**"), or any corresponding application for Regulatory Approval in the Territory, including, with respect to the European Union, a marketing authorization application ("**MAA**") filed with the EMA pursuant to the Centralized Approval Procedure or an MAA filed with the PMDA, including, in each case, all supplements, amendments, variations, extensions and renewals thereof.

1.50 "**Effective Date**" means the first Business Day following the HSR Clearance Date.

1.51 "**EMA**" means the European Medicines Agency and any successor agency(ies) or authority having substantially the same function.

1.52 "**European Union**" means the economic, scientific, and political organization of member states known as the European Union, as its membership may be altered from time to time, and any successor thereto.

1.53 "**Exploit**," "**Exploitation**" or "**Exploiting**" means to make, have made, import, export, use, have used, sell, have sold, or offer for sale, including to Develop, Commercialize, register, modify, enhance, improve, Manufacture, have Manufactured, hold, or keep (whether for disposal or otherwise) or otherwise dispose of. "**Exploited**" has a corresponding meaning.

1.54 "**FDA**" means the United States Food and Drug Administration and any successor agency(ies) or authority having substantially the same function.

1.55 "**FFDCA**" means the United States Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.*, as amended from time to time, together with any rules, regulations and requirements promulgated thereunder (including all additions, supplements, extensions and modifications thereto).

1.56 "**Field**" means any and all uses or applications.

1.57 "**First Commercial Sale**" means, with respect to a Product and a country, the first sale for monetary value for use or consumption by the end user of such Product in such country after Regulatory Approval for such Product has been obtained in such country and where such sale results in a recordable Net Sale in accordance with the applicable Accounting Standards. Sales prior to receipt of Regulatory Approval for such Product, such as so-called "treatment IND sales," "named patient sales," and "compassionate use sales," in each case to the extent such Licensed Product is sold at or below cost, shall not be construed as a First Commercial Sale.

1.58 "**First Co-Commercialization Drug Approval Application**" means a Drug Approval Application for a CNS Product that: (a) is filed by Sanofi (or its Affiliate) in the U.S. or China, as the case may be, and accepted for substantive review by the applicable Regulatory Authority in such country; (b) is the first Drug Approval Application to be filed in such country with respect to such CNS Product; and (c) is for an Indication within the Neurology Field, other than an Indication within Multiple Sclerosis.

1.59 "**FTE**" means the equivalent of the work of one (1) person full time for one (1) Calendar Year (consisting of at least a total of [***] hours per Calendar Year). Each employee or, if applicable, with respect to Co-Commercialization Activities only, contractor, utilized by a Party in connection with its performance under this Agreement may be less than or equal to one FTE based on the hours actually worked by such employee or contractor performing Development, Commercialization or Manufacturing activities, as applicable, with respect to a Program and shall be treated as an FTE on a *pro rata* basis based upon the actual number of such hours worked, up to a maximum of [***]. For avoidance of doubt, the FTE Rate applicable to any such contractor performing Co-Commercialization Activities shall be determined accordance with the provisions of **Section 1.61** ("FTE Rate" definition) and subject to **Section 5.4.2** (Calculation of Sales Force Costs).

1.60 "**FTE Costs**" means, with respect to a Party for any period, the applicable FTE Rate multiplied by the applicable number of FTEs of such Party performing Development or Commercialization activities during such period in accordance with the applicable CNS Development Plan, Additional CNS Development Proposal or Co-Commercialization Budget, as the case may be.

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1.61 "**FTE Rate**" means the applicable rate specified on **Schedule 1.61** for the relevant category of FTEs with respect to Development or Commercialization activities, as applicable, conducted under the Agreement by or on behalf of a Party, which rate, in each case, shall be adjusted annually, effective as of January 1 of each Calendar Year and with the first such annual adjustment to be made as of January 1, 2019, by the total percentage change in the [***] for the 12 month period preceding each such January 1, unless the Parties otherwise mutually agree. Except as specified in **Section 1.6** ("Allowable Expenses" definition), all internal and out-of-pocket costs and expenses associated with travel, training, hiring and administration that are not specific to a Compound or Product are included within each FTE Rate and will not be charged separately as a Development Cost or Allowable Expense. It is understood that the FTE Rates for FTEs with respect to Commercialization activities conducted under this Agreement shall (a) [***], and (b) [***].

1.62 "**Generic Version**" means, with respect to a particular Product and a particular country, any small molecule pharmaceutical product (a) that is sold by a Person other than a Party or its Affiliates or Sublicensees, which Person did not purchase such product in a chain of distribution that included such Party or its Affiliate or Sublicensee as intentional participants, (b) contains the same or a bioequivalent RIPK1 Inhibitor as such Product, and (c) whose Regulatory Approval is approved by a Regulatory Authority solely in reliance on the prior approval of such Product [***].

1.63 "**Global Commercialization Plan**" means, for each Program, the global commercialization plan for the Commercialization of Products included in such Program in the Field in the Territory, as described in **Section 5.3.1** (Global Commercialization Plan).

1.64 "**Good Clinical Practices**", "**GCP**" or "**cGCP**" means the then-current standards, practices and procedures promulgated or endorsed by the FDA as set forth in the guidelines adopted by the International Conference on Harmonization ("**ICH**"), titled "*Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance"*, (or any successor document) including related regulatory requirements imposed by the FDA and comparable regulatory standards, practices and procedures promulgated by the EMA, PMDA or other Regulatory Authority applicable to the Territory, as they may be updated from time to time.

1.65 "**Good Laboratory Practices**", "**GLP**" or "**cGLP**" means the then-current standards, practices and procedures promulgated or endorsed by the FDA as set forth in 21 C.F.R. Part 58 (or any successor statute or regulation), including related regulatory requirements imposed by the FDA and comparable regulatory standards, practices and procedures promulgated by the EMA, PMDA or other Regulatory Authority applicable to the Territory, as they may be updated from time to time, including applicable guidelines promulgated under the ICH.

1.66 "**Good Manufacturing Practice**", **GMP**" or "**cGMP**" means the then-current good manufacturing practices required by the FDA, as set forth in the FFDCA, as amended, and the regulations promulgated thereunder, for the manufacture and testing of pharmaceutical materials, and comparable Applicable Law related to the manufacture and testing of pharmaceutical materials in jurisdictions outside the U.S., including the quality guideline promulgated by the ICH designated ICH Q7A, titled "*Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*" and the regulations promulgated thereunder, in each case as they may be updated from time to time.

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1.67 "**HSR Act**" means the Hart-Scott-Rodino Antitrust Improvements Act of 1976, as amended.

1.68 [***].

1.69 "**In-License Agreement**" means any agreement between a Party and a Third Party pursuant to which such Party has obtained rights to any Third Party intellectual property which is reasonably necessary or actually used to Exploit a CNS Compound or CNS Product pursuant to this Agreement.

1.70 "**IND**" means an application filed with a Regulatory Authority for authorization to commence Clinical Studies, including (a) an Investigational New Drug Application as defined in the FFDCA or any successor application or procedure filed with the FDA, (b) any equivalent of a United States IND in other countries or regulatory jurisdictions (*e.g.*, Clinical Trial Application (CTA)), and (c) all supplements, amendments, variations, extensions and renewals thereof that may be filed with respect to the foregoing.

1.71 "**Indication**" means a disease or condition and all of its associated signs, symptoms, stages or progression (including precursor conditions), [***].

1.72 "**Information**" means all knowledge of a technical, scientific, business and other nature, including know-how, inventions, technology, methods, processes, practices, formulae, instructions, skills, techniques, procedures, experiences, ideas, technical assistance, designs, drawings, assembly procedures, computer programs, specifications, data, results and similar material, Regulatory Data, and other biological, chemical, pharmacological, toxicological, pharmaceutical, physical and analytical, pre-clinical, clinical, safety, manufacturing and quality control data and information, including study designs and protocols, materials, reagents (*e.g.*, plasmids, proteins, cell lines, assays and compounds) and biological methodology; in each case (whether or not confidential, proprietary, patented or patentable, of commercial advantage or not) in written, electronic or any other form now known or hereafter developed.

1.73 "**Initial CNS Development Plan**" means the CNS Development Plan as of the Execution Date and attached as **Schedule 1.73**.

1.74 "**Initial CNS Development Budget**" means the CNS Development Budget as of the Execution Date and attached as **Schedule 1.74**.

1.75 "**Initial Peripheral Development Plan**" means the Peripheral Development Plan as of the Execution Date and attached as **Schedule 1.75**.

1.76 "**Initiation**" means, with respect to any Clinical Study, the [***] in such Clinical Study. "**Initiate**" means to engage in Initiation and "**Initiated**" has a corresponding meaning.

1.77 "**Joint Committee**" means the JSC, JDC or JCC, as applicable.

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1.78 "**Joint Program Know-How**" means any proprietary Information that is generated jointly by one or more employees, consultants or contractors of each of Denali and Sanofi, or their respective Affiliates, in the performance of activities with respect to the Development, Manufacture, Commercialization or other Exploitation of any Compound(s) or Product(s) under this Agreement during the Term or during any post-termination transition activities conducted pursuant to **Section 13.8** (Effects of Termination), as determined pursuant to **Section 8.1.1** (Ownership of Patents and Know-How Generated under this Agreement).

1.79 "**Joint Program Patent**" means any Program Patent that Covers an invention or discovery conceived jointly by one or more employees, consultants or contractors of each of Denali and Sanofi, or their respective Affiliates, in the performance of activities with respect to the Development, Manufacture, Commercialization or other Exploitation of any Compound(s) or Product(s) under this Agreement during the Term or during any post-termination transition activities conducted pursuant to **Section 13.8** (Effects of Termination), as determined pursuant to **Section 8.1.1** (Ownership of Patents and Know-How Generated under this Agreement).

1.80 "**Licensed Compound**" means any CNS Licensed Compound or Peripheral Licensed Compound.

1.81 "**Licensed Product**" means a CNS Licensed Product or a Peripheral Licensed Product.

1.82 "**Major Markets**" means the United States, France, Germany, Italy, Spain, the United Kingdom, China and Japan.

1.83 "**Major Market Regulatory Filings**" means all INDs, pre-meeting submissions, Drug Approval Applications, Product Labeling, material labeling supplements, Regulatory Authority meeting requests, core data sheets, investigator brochures and other material regulatory submissions, in each case, in the Major Markets.

1.84 "**Manufacture**," "**Manufacturing**" and "**Manufactured**" means all activities related to the synthesis, making, production, processing, purifying, formulating, filling, finishing, packaging, labeling, shipping and storage of a Compound, a Product, or any intermediate of any of the foregoing, including process development, process qualification and validation, scale-up, pre-clinical, clinical and Commercial production and analytic development, product characterization, stability testing, quality assurance and quality control.

1.85 "**Manufacturing Cost**" means, with respect to a Compound or Product, the [***] cost incurred by a Party or an Affiliate of a Party for Manufacturing or purchasing from a Third Party, as applicable, Compounds and Products, in each case, only to the extent allocable to such Manufacture (including (a) [***] and (b) [***], calculated as follows:

1.85.1 with respect to purchases of Compounds or Products from a Third Party, [***]; plus [***] under this **Section 1.85.1**.

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1.85.2 with respect to Manufacturing of Compounds or Products by a Party or its Affiliate, [***]; plus [***].

1.85.3 [***].

1.85.4 Notwithstanding the foregoing, in the case of **Sections 1.85.2** and **1.85.3**, the Manufacturing Costs or Standard Cost, if applicable, [***], all as determined by the Finance Working Group (with input from the Manufacture Working Group). For such purposes, a [***].

1.86 "**Material Safety Event**" means [***], in each case, [***] or [***], and [***].

1.87 "**MSL Activities**" means field-based activities conducted by personnel designated as medical science liaisons (or similar title), whether before or after commercial launch of a Product, including (a) providing scientific data about the Products and disease state to healthcare providers and the various constituents therein, including clinicians, nurses, pharmacists and others, through in-person meetings and presentations or other methods; (b) collecting feedback from healthcare providers and the various constituents therein regarding their questions and scientific data needs related to the Products and disease state, through in-person meetings and presentations or other methods; (c) attending medical meetings that involve the Product or its targeted Indication(s); (d) delivering presentations on a Product, its method of administration or its effects; (e) developing and maintaining relationships with leading physicians or key opinion leaders in the treatment of the Indications targeted by a Product; (f) liaising with health care providers regarding investigator-initiated studies related to a Product, Phase IV Marketing Studies related to a Product and other data generation opportunities involving the Product; and (g) in appropriate circumstances, training the sales force on a Product.

1.88 "**Multiple Sclerosis**" means an Indication [***].

1.89 "**Net Revenues**" means, with respect to all Cost Profit Sharing Product(s) in a Cost Profit Sharing Country and, if applicable for one or more particular Cost Profit Sharing Product(s), accrued prior to the Co-Funding End Date following Denali's exercise of the Denali Royalty Option pursuant to **Section 7.8** (Denali Royalty Option): (a) the total Net Sales of all Cost Profit Sharing Product(s) in such Cost Profit Sharing Country, *plus* (b) Other Income with respect to such Cost Profit Sharing Product(s) in such Cost Profit Sharing Country.

1.90 "**Net Sales**" means, with respect to a Product for any period, the total amount billed or invoiced on sales of such Product during such period by a Party, its Affiliates, or Sublicensees in the Territory to Third Parties (including Third Party wholesalers or distributors), in bona fide arm's length transactions, less the following deductions, in each case related specifically to such Product and actually allowed and taken by such Third Parties and not otherwise recovered by or reimbursed to such Party, its Affiliates or Sublicensees, to the extent deducted in accordance with the applicable Accounting Standards of the Party and its Affiliates consolidating the sales in calculating the "gross to net" revenue adjustment:

1.90.1 discounts, including cash, trade and quantity discounts, in each case related specifically to such Product;

1.90.2 price reductions programs including co-pay assistance, compulsory refunds and any other patient payment assistance programs, retroactive price adjustments with respect to sales of a Product, charge-back payments and rebates granted to managed health care organization or to federal state and local government (or their respective agencies, purchasers and reimbursers) or to trade customers, including wholesalers and chain and pharmacy buying groups, in each case related specifically to such Product;

1.90.3 Taxes, duties on sales such as sales, value added, use taxes to the extent added to the sale price and set forth separately as such in the total amount invoiced and [***];

1.90.4 amounts repaid or credited by reason of rejections, recalls, damaged products, expired dating, refunds, billing errors, defects, free goods allowance, recalls or returns, or because of retroactive price reductions, including rebates or wholesaler charge backs, in each case related specifically to such Product;

1.90.5 the portion of administrative fees paid during the relevant time period to group purchasing organizations, pharmaceutical benefit managers or Medicare Prescription Drug Plans, in each case to the extent relating to such Product;

1.90.6 any invoiced amounts for Product from a prior period which are not collected and are written off by a Party or its Affiliates in accordance with IFRS, [***]; and

1.90.7 (a) freight, insurance, import/export and other transportation charges (including customs duties, surcharge and other governmental charges incurred in connection with the exportation or importation of a Product) to the extent added to the sale price and set forth separately as such in the total amount invoiced, and (b) fees for services provided by wholesalers and warehousing chains related to the distribution of such Product, such fees being calculated at their actual cost.

Net Sales shall not include transfers or dispositions without charge or for a price equal to or less than Manufacturing Cost for charitable, promotional, pre-clinical, clinical, regulatory or governmental purposes. Net Sales shall include the amount or fair market value of all other consideration received by a Party, its Affiliates or Sublicensees in respect of sales of a Product, whether such consideration is in cash, payment in kind, exchange or other form. Net Sales shall not include sales of Product between or among a Party, its Affiliates or Sublicensees for resale, but the subsequent resale of such Product to a Third Party shall be included within the computation of Net Sales. For purposes of determining Net Sales, a Product shall be deemed to be sold when recorded as a sale in accordance with the applicable Accounting Standards. For clarity, a particular deduction may be accounted for only once in the calculation of Net Sales or, to the extent applicable, in the calculation of Allowable Expenses and Net Revenue. For the avoidance of doubt, and for all purposes under this Agreement, Net Sales shall be accounted for in accordance with Accounting Standards, as practiced in the relevant country in the Territory, but in any event in accordance with the applicable Accounting Standards, as consistently applied by such Party in such country in the Territory.

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On a country-by-country basis, in the event a Product is sold as a Combination Product, Net Sales will be calculated by [***].

With respect to any Combination Product where: (a) the Other Active Ingredient is not sold separately in the applicable country during the applicable accounting period; or (b) a Product containing the applicable Compound is not sold separately in the applicable country during the applicable accounting period, then [***].

In the event Sanofi or any of its Affiliates or Sublicensees sell a Product to a Third Party who also purchases other products or services from Sanofi or such Affiliate or Sublicensee, as applicable, and Sanofi or such Affiliate or Sublicensee discounts the purchase price of such Product to a greater degree than Sanofi or such Affiliate or Sublicensee generally discounts the price of their other products or services to such customer, then, in such case, the Net Sales of the applicable Product to such Third Party shall be deemed to be equal to the arm's length price that Third Parties would generally pay for such Product alone when not purchasing any other product or services from Sanofi or its Affiliate or Sublicensee.

1.91 "**Neurology Field**" means [***] In any event, [***].

1.92 "**Non-Development Lead**" means the Party that is not the Development Lead.

1.93 "**Non-Regulatory Lead**" means the Party that is not the Regulatory Lead.

1.94 "**Operational Matter**" means, [***].

1.95 "**Opt-in Premium Rate**" means: (a) [***]; and (b) [***].

1.96 "**Other Active Ingredient**" means any standalone active pharmaceutical ingredient that [***]. For purposes of clarity, specifically excluded from "Other Active Ingredients" are: (x) delivery technologies that increase delivery or exposure of compounds in the brain or provide for tissue or cell targeting; and (y) components or modifications to a Compound or Product, or formulation thereof, that provide additional pharmacological activity or altered pharmacokinetic qualities (including adjuvants or excipients improving solubility, stability or bioavailability).

1.97 "**Other Income**" means any payment (other than Net Sales) when recognized as income or an offset to an expense in accordance with the applicable Accounting Standards by a Party or its Affiliate from a Third Party that is reasonably attributable to a Cost Profit Sharing Product in a Cost Profit Sharing Country, including any such payment received in connection with the grant of a sublicense or other right or activity with respect to a Cost Profit Sharing Product in a Cost Profit Sharing Country, including the grant of an option to obtain such sublicense or other right with respect to a Cost Profit Sharing Product in a Cost Profit Sharing Country. For clarity, any portion of such payment that is recognized by a Party as an offset to an expense and recorded as Other Income as part of the quarterly reconciliation and true-up process in accordance with **Section 7.7.5** (Reporting, Recognition and True-Up), shall not also be recorded as an offset against Shared Development Costs or Allowable Expenses for the purposes of such reconciliation and true-up.

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1.98 "**Out-of-Pocket Costs**" means amounts actually paid to Third Party vendors or contractors, for services or materials. For clarity, to be included as part of the Shared Development Costs, the foregoing shall be either: (a) provided by such Person directly in the performance of activities under and in accordance with a CNS Development Plan or Co-Commercialization Plan and in accordance with the associated CNS Development Budget or Co-Commercialization Budget, as applicable; or (b) applicable directly to a Compound, a Product or a Program and for which this Agreement provides that such costs are sharable or allocable between the Parties as a Shared Development Cost, Allowable Expense or otherwise. For clarity, except to the extent provided for in **Section 1.6** ("Allowable Expenses" definition), Out-of-Pocket Costs do not include payments for the following internal costs: salaries or benefits; travel, training or hiring; facilities; utilities; general office or facility supplies; insurance; information technology, capital expenditures; market research or the like.

1.99 "**Patents**" means: (a) all national, regional and international patents and patent applications, including provisional patent applications, including utility models, industrial designs and certificates of invention and applications for the foregoing; (b) all applications filed either from any of the foregoing or from an application claiming priority from any of the foregoing, including divisionals, continuations, continuations-in-part, provisionals, converted provisionals and continued prosecution applications or other pre-grant forms; (c) any and all patents, utility models, industrial designs and certificates of invention that have issued or in the future issue from the foregoing applications (*i.e.*, described in clauses (a) and (b) above); and (d) any and all extensions or restorations by existing or future extension or restoration mechanisms or other post-grant forms of any of the foregoing, including revalidations, reissues, re-examinations and extensions (including any supplementary protection certificates and the like) of the foregoing (*i.e.*, described in clauses (a), (b), and (c) above).

1.100 "**Patient Safety Risk**" means [***].

1.101 "**Peripheral Compound**" means a Peripheral Licensed Compound or a Sanofi Peripheral Compound.

1.102 "**Peripheral Development Plan**" means the plan for the Development of Peripheral Compounds and Peripheral Products, as described in **Section 3.2.1(c)** (Content of Peripheral Development Plan).

1.103 "**Peripheral Licensed Compound**" means: (a) each of the small molecule compounds known internally at Denali as "**DNL758**", [***]; and (b) any RIPK1 Inhibitor that (i) (A) [***], or (B) [***]; (ii) [***]; but excluding, in each case, any [***].

1.104 "**Peripheral Licensed Product**" means any product containing, alone or in combination with one or more Other Active Ingredients, a Peripheral Licensed Compound, in any formulation, dosage strength or method of delivery.

1.105 "**Peripheral Product**" means a Peripheral Licensed Product or a Sanofi Peripheral Product.

1.106 "**Peripheral Program**" means all Peripheral Compounds and Peripheral Products, and the Development activities, Manufacturing activities and Commercialization activities with respect to such Peripheral Compounds and Peripheral Products.

1.107 "**Person**" means an individual, sole proprietorship, partnership, limited partnership, limited liability partnership, corporation, limited liability company, business trust, joint stock company, trust, unincorporated association, joint venture or other similar entity or organization, including a government or political subdivision, department or agency of a government.

1.108 "**Phase I Trial**" means a human clinical trial of a Compound or Product, the principal purpose of which is a preliminary determination of safety, tolerability or pharmacokinetics in healthy individuals or patients or similar clinical study prescribed by the Regulatory Authorities, including the trials referred to in 21 C.F.R. §312.21(a), as amended (and any equivalent Clinical Study in any jurisdiction outside the United States).

1.109 "**Phase II Trial**" means a human clinical trial of a Compound or Product, the principal purpose of which is to explore efficacy, pharmacodynamics or biological activity in one (1) or more specified doses in the target patient population, or a similar clinical study recommended by the Regulatory Authorities, from time to time, pursuant to Applicable Law or otherwise, including the trials referred to in 21 C.F.R. §312.21(b), as amended (and any equivalent Clinical Study in any jurisdiction outside the United States). For clarity, [***].

1.110 "**Phase III Trial**" means a human clinical trial of a Compound or Product on a sufficient number of subjects in an indicated patient population that is designed to establish that a Compound or Product is safe and efficacious for its intended use and to determine the benefit/risk relationship, warnings, precautions, and adverse reactions that are associated with such product in the dosage range to be prescribed, which trial is intended to support a Regulatory Approval for such Compound or Product, including all tests and studies that are required by the applicable Regulatory Authority from time to time, pursuant to Applicable Law or otherwise, including the trials referred to in 21 C.F.R. §312.21(c), as amended (and any equivalent Clinical Study in any jurisdiction outside the United States). Without limiting the foregoing, [***].

1.111 "**Phase IV Development Study**" means a post-approval clinical study for a Product with respect to any Indication for which Regulatory Approval has been received in a particular country and that is required by a Regulatory Authority in such country, or agreed with a Regulatory Authority to be conducted, as a condition of receiving or maintaining such Regulatory Approval.

1.112 "**Phase IV Marketing Study**" means a clinical study for a Product with respect to any Indication for which Regulatory Approval has been received in a particular country and that is not Phase IV Development Study.

1.113 "**PMDA**" means Japan's Pharmaceuticals and Medical Devices Agency and any successor agency(ies) or authority having substantially the same function.

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1.114 "**Post-Grant Examination Proceedings**" means proceedings conducted with respect to a Patent before a patent office or other administrative agency that is not a court of law and that has jurisdiction to grant and review such Patent following the grant or issuance of such Patent and pursuant to which the validity, enforceability or scope of such Patent is challenged by a Third Party, including a post-grant opposition proceeding, *ex parte* re-examination (but only if such re-examination is requested by a Third Party), *inter partes* review and other post-grant review proceedings. An appeal, including to a court of law, from such Post-Grant Examination Proceeding, shall be understood to be encompassed by the term Post-Grant Examination Proceedings.

1.115 "**Product**" means a Peripheral Product or a CNS Product.

1.116 "**Product Labeling**" means, with respect to a Product in a country or other jurisdiction in the Territory, (a) the full prescribing information for such Product for such country or other jurisdiction, including any required patient information, approved by the applicable Regulatory Authority; and (b) all labels and other written, printed, or graphic matter upon a container, wrapper, or any package insert utilized with or for such Product in such country or other jurisdiction.

1.117 "**Product Patents**" means [***].

1.118 "**Product Trademarks**" means the product specific Trademark(s) to be used by a Party or its Affiliates or its or their respective Sublicensees for the Development or Commercialization of Products in the Territory and any registrations thereof or any pending applications relating thereto in the Territory (excluding, in any event, any trademarks, service marks, names or logos that include any Corporate Name or logo of the Parties or their Affiliates, including the Corporate Names of the Parties). For the avoidance of doubt, any Trademark or proposed Trademark evaluated for use as Product Trademark but not actually used in the Commercialization of a Product shall not be a Product Trademark.

1.119 "**Program Patent**" means [***].

1.120 "**Programs**" means the CNS Program and the Peripheral Program.

1.121 "**Prosecution and Maintenance**" (including variations such as "**Prosecute and Maintain**") means, with respect to a Patent or to a Product Trademark, the preparation, filing, prosecution and maintenance of such Patent or such Product Trademark, including payment of all maintenance or governmental fees to maintain such Patent or such Product Trademark in force, and requests for patent term extensions, supplementary protection certificates and the like with respect to such Patent, together with the conduct of interferences, Post-Grant Examination Proceedings and other similar proceedings with respect to a Patent, but excluding any Post-Grant Examination Proceedings initiated [***].

1.122 "**Regulatory Approval**" means, with respect to a country or other jurisdiction in the Territory, all approvals (including approvals of Drug Approval Applications), licenses, registrations or authorizations of any Regulatory Authority necessary to Commercialize a Compound or Product in such country or other jurisdiction, including, where applicable, (a) pricing

or reimbursement approval in such country or other jurisdiction, and (b) approval of Product Labeling.

1.123 "**Regulatory Authority**" means any applicable supra-national, federal, national, regional, state, provincial or local governmental or regulatory authority, agency, department, bureau, commission, council or other entities (*e.g.*, the FDA, EMA and PMDA) regulating or otherwise exercising authority with respect to activities contemplated in this Agreement, including the Exploitation of a Compound or Product in any portion of the Territory.

1.124 "**Regulatory Documentation**" means all: (a) applications (including all INDs and Drug Approval Applications and other Major Market Regulatory Filings), registrations, licenses, authorizations, and approvals (including Regulatory Approvals) and designations (including designations of a product as an "orphan" drug or its equivalent outside of the United States); (b) correspondence, materials and reports submitted to or received from Regulatory Authorities (including pre-meeting submissions, minutes and official contact reports relating to any communications with any Regulatory Authority and reports issued by a Regulatory Authority in connection with any audit conducted by such Regulatory Authority) and all supporting documents with respect thereto, including all regulatory drug lists, advertising and promotion documents, adverse event files, and complaint files (including product technical complaints communications and handling); and (c) Clinical Data and data contained or relied upon in any of the foregoing, in each case (*i.e.*, clauses (a), (b), and (c) above), to the extent pertaining to a Compound or Product.

1.125 "**Regulatory Exclusivity**" means, with respect to any country or jurisdiction, any exclusive marketing rights or data exclusivity protection conferred by an applicable Regulatory Authority or other governmental body in such country or jurisdiction with respect to a compound or pharmaceutical product, including any regulatory data protection exclusivity (including any orphan drug designation or pediatric exclusivity) and any extensions to such exclusivity rights.

1.126 "**Regulatory Lead**" means the Party specified as the "Regulatory Lead" in **Section 3.4.2** (CNS Program Regulatory Lead).

1.127 "**Related Compound**" means [***].

1.128 "**Right of Reference**" means the right to allow a Regulatory Authority or a Party to rely upon the Clinical Data and other Information from Clinical Studies or other Development activities that are in the possession of a Regulatory Authority for the purpose of seeking, obtaining or maintaining Regulatory Approval, including the ability to allow such Regulatory Authority to review the underlying raw data as part of an investigation by such Regulatory Authority, if necessary.

1.129 "**RIPK1**" means [***].

1.130 "**RIPK1 Inhibitor**" means any small molecule: [***].

1.131 "**Sanofi CNS Compound**" means, subject to **Section 6.8.2(b)** (Change in Control Competing Product), any RIPK1 Inhibitor that is a CNS Penetrant Compound that: (a) (i) [***], or (ii) [***]; (b) [***]; or (c) [***]; but excluding in each case any [***].

1.132 "**Sanofi CNS Development Activities**" means [***].

1.133 "**Sanofi CNS Product**" means any product containing, alone or in combination with one or more Other Active Ingredients, a Sanofi CNS Compound, in any formulation, dosage strength or method of delivery.

1.134 "**Sanofi Compound**" means a Sanofi CNS Compound or a Sanofi Peripheral Compound.

1.135 "**Sanofi Know-How**" means proprietary Information, including any related Regulatory Documentation and Clinical Data, Controlled by Sanofi or any of its Affiliates (a) as of the Effective Date or during the Term and that is reasonably necessary or reasonably useful for the Development, Manufacture, Commercialization or other Exploitation of Sanofi Compounds or Sanofi Products; or (b) generated by or on behalf of Sanofi or any of its Affiliates in the performance of the activities with respect to the Development, Manufacture, Commercialization or other Exploitation of any Compound(s) or Product(s) under this Agreement during the Term or during any post-termination transition activities conducted pursuant to **Section 13.8** (Effects of Termination), including Sanofi's interest in any Joint Program Know-How.

1.136 "**Sanofi Patents**" means Patents Controlled by Sanofi or any of its Affiliates (a) issued or filed before, on or after the Effective Date and during the Term, that are reasonably necessary or reasonably useful for the Development, Manufacture, Commercialization or other Exploitation of Sanofi Compounds or Sanofi Products, including diagnostic tools or biomarkers pertaining thereto; or (b) Covering inventions or discoveries conceived by or on behalf of Sanofi or any of its Affiliates in the performance of activities with respect to the Development, Manufacture, Commercialization or other Exploitation of any Compound(s) or Product(s) under this Agreement during the Term or during any post-termination transition activities conducted pursuant to **Section 13.8** (Effects of Termination). For clarity Product Patents, Program Patents, and Joint Program Patents to the extent Controlled by Sanofi or any of its Affiliates and, in each case that meet the foregoing requirements of clause (a) or (b) are Sanofi Patents.

1.137 "**Sanofi Peripheral Compound**" means, subject to **Section 6.8.2(b)** (Change in Control Competing Product), any RIPK1 Inhibitor that is not a CNS Penetrant Compound that: (a) (i) [***], or (ii) [***]; (b) [***]; or (c) [***]; but excluding in each case, any [***].

1.138 "**Sanofi Peripheral Product**" means any product containing, alone or in combination with one or more Other Active Ingredients, a Sanofi Peripheral Compound, in any formulation, dosage strength or method of delivery.

1.139 "**Sanofi Product**" means a Sanofi CNS Product or a Sanofi Peripheral Product.

1.140 "**[***]**" means [***].

1.141 "**Sanofi Technology**" means, collectively, the Sanofi Patents and the Sanofi Know-How.

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1.142 "**Segregate**" means, with respect to a Competing Product, as applicable, the execution by a Party (or its successor) of a plan developed in good faith by such Party to segregate the Development, Manufacture and Commercialization activities relating to such Competing Product, as applicable, from Development, Manufacture and Commercialization activities with respect to Compounds and Products under this Agreement, including using reasonable efforts to ensure that: (a) [***]; and (b) [***]; *provided* that, in either case of (a) or (b), [***].

1.143 "**Shared Development Costs**" means those Development Costs incurred by or on behalf of a Party in accordance with the CNS Development Plan and the corresponding CNS Development Budget, as such plan and budget may be revised from time to time in accordance with the terms of this Agreement, to the extent specifically identifiable or reasonably allocable to the Development of CNS Compounds or CNS Products, except as provided in **Section 3.2.4** (Additional CNS Program Development Activities) or **Section 7.8** (Denali Royalty Option) and always excluding any Excess Study Costs. Subject to the foregoing, Shared Development Costs include the following:

1.143.1 Development Costs incurred in connection with Phase III Trials and Phase IV Development Studies conducted as part of the CNS Program in accordance with the CNS Development Plan (such trials, "**Shared Cost Trials**"), except as provided in **Section 3.2.4** (Additional CNS Program Development Activities) or **Section 7.8** (Denali Royalty Option) and exclusive of any Excess Study Costs;

1.143.2 Indemnified Losses and other Out-of-Pocket Costs incurred in connection with Third Party Claims described in **Section 12.3** (Certain Indemnified Losses) solely to the extent such Indemnified Losses and other Out-of-Pocket Costs are specified in **Section 12.3** (Certain Indemnified Losses) as to be included in Shared Development Costs; and

1.143.3 any other FTE Costs and Out-of-Pocket Costs agreed to be shared by the Parties as a Shared Development Cost as expressly set forth in this Agreement or as may be otherwise mutually agreed in writing by the Parties.

For clarity: (A) Development Costs are exclusive of, and do not include, Allowable Expenses (and *vice versa*); and (B) Development Costs shall not include any FTE Costs, Out-of-Pocket Costs or Manufacturing Costs with respect to any item described in **Section 1.143.1** or **Section 1.143.2** incurred after the Co-Funding End Date for a Cost Profit Sharing Opt Out Product in its corresponding Cost Profit Sharing Opt Out Country.

[***].

1.144 "**Subcontract Agreement**" means, with respect to a Third Party Provider, a written agreement between a Party and such Third Party Provider.

1.145 "**Sublicensee**" means a Person that is granted (directly or indirectly) (a) a sublicense by a Party or its Affiliate under any of the rights granted in **Section 6.1** (License Grants to Sanofi) or **Section 6.2** (License Grants to Denali), as applicable; or (b) in the case of a Sanofi Compound or Sanofi Product and solely for purposes of **Section 1.62** ("Generic Version" definition), **Section**

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1.90 ("Net Sales" definition), **Section 1.118** ("Product Trademark" definition), **Section 6.3** (Sublicenses; Licensing), **Section 8.1.2** (Assignment, Disclosure and Assistance Obligation), **Section 8.4** (Infringement Claims by Third Parties), clause (a) of **Section 12.1** (Indemnification of Denali), **[***]**, and **Section 15.15** (Performance by Affiliates, Sublicensees and Third Party Providers), a license under the Sanofi Technology to Develop or Commercialize such Sanofi Compound or Sanofi Product; in each case, and in accordance with **Section 6.3** (Sublicenses; Licensing).

1.146 "**Tax**" or "**Taxes**" means any form of tax or taxation, levy, duty, charge, social security charge, contribution or withholding of whatever nature (including any related fine, penalty, surcharge or interest) imposed by, or payable to, any government, state or municipality, or any local, state, federal or other fiscal, revenue, customs or excise authority, body or official in the Territory.

1.147 "**Territory**" means the entire world.

1.148 "**Terminated Product**" means a Terminated Denali Product or Terminated Sanofi Product.

1.149 "**Third Party**" means any Person other than Denali, Sanofi and their respective Affiliates.

1.150 "**Third Party Provider**" means a Third Party service provider to which a Party has subcontracted its activities under and in accordance with this Agreement.

1.151 "**Trademark**" means any word, name, symbol, color, designation or device or any combination thereof that functions as an identifier of the source or origin of goods or services, including any trademark, trade dress, brand mark, service mark, trade name, brand name, logo, business symbol or domain names, whether or not registered.

1.152 "**Transition Plan**" means the plan, approved by the Parties, for the transfer of the Development Lead and Regulatory Lead from one Party to the other Party under with respect to a particular CNS Product, which plan will set forth those activities necessary to transition relevant responsibilities with respect to such CNS Product (and any CNS Compound contained in such CNS Product), including the transfer of regulatory responsibilities and pharmacovigilance responsibilities.

1.153 "**United States**" or "**U.S.**" means the United States of America and its territories and possessions (including the District of Columbia and Puerto Rico).

1.154 "**Valid Claim**" means [***].

1.155 **Additional Definitions**. In addition, each of the following terms shall have the meaning described in the corresponding Section of this Agreement identified below.

Term	**Section**
3 Tox Study	3.2.3(a)(v)
6/9 Tox Study	3.2.3(a)(iv)

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Term	Section
Additional Activity Regulatory Approval Application	3.2.4(e)(iv)
Additional CNS Development Activities	3.2.4
Additional CNS Development Opt-In Notice	3.2.4(e)(i)
Additional CNS Development Proposal	3.2.4(a)
Additional CNS Development Study	3.2.4
ADR	15.6.1
Adverse Co-Commercialization Ruling	Schedule 5.2.4
Adverse Ruling	13.2
Affected Activities	Schedule 5.2.4
Agreement	Preamble
Alliance Manager	2.6
Arbitrator / Arbitrators	15.6.3(b)
Auditor	Schedule 5.2.4
Balancing Payment	7.7.5
Bankruptcy Code	13.11
Breaching Party	13.2
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
Calendar Period	Schedule 5.2.4
Challenge Proceeding	Schedule 6.5.1
Change in Control Effective Date	6.8.2(b)
CMO Supply Agreement	4.1
CNS Development Budget	3.2.1(b)(ii)
CNS Milestone	7.2.1
CNS Milestone Payments	7.2.1
CNS Patient Samples	3.7
CNS Phase I Trials	3.2.3(iv)
Co-	5.2.4(a)

Term	Section
Co-Commercialization Operational Plan	Schedule 5.2.4
Co-Commercialization Option	5.2.4(a)
Co-Commercialization Product	5.2.4
Co-Commercialization Term	Schedule 5.2.4
Co-Commercialization Territory	5.2.4(a)
Co-Funding Amount	7.8.2
Co-Funding End Date	7.8.1
[***]	[***]
Commercialization Wind-down Period	13.8.1(f)(ii)
Comparable Third Party CMO	1.85.4
Competing Product	6.8.2(a)
Competing Product Election Notice	6.8.2(b)
Convicted Entity	11.1.5(d)
Convicted Individual	11.1.5(d)
Corrective Plan	Schedule 5.2.4
Cost Cap	7.7.2(c)
Cost Profit Sharing	7.7
Cost Profit Sharing Country	7.7
Cost Profit Sharing Opt Out Country	7.8.1
Cost Profit Sharing Opt Out Products	7.8.1
Cost Profit Sharing Product	7.7
CRM	5.4.1(e)
Data Room	11.2.5
Debarred Entity	11.1.5(b)
Debarred Individual	11.1.5(a)
Declining Party	3.2.4(c)
Default Notice	13.2
Denali	Preamble
Denali Activities Range	5.2.4(a)
Denali Controlled Denali Patents	11.2.6
Denali	13.8.1(f)(i)

Commercialization Activities		Development Wind-Down Period	
Co-Commercialization Agreement	5.2.4(b)	Denali Indemnitees	12.1
Co-Commercialization Country	5.2.4(a)	Denali Licensed Patents	11.2.6

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Term	Section
Denali New Peripheral Program Technology Terms	6.5.2(b)(i)
Denali Royalty Option	7.8.1
Denali Unblocking Know-How	13.8.4(a)(ii)
Denali Unblocking Patent Rights	13.8.4(a)(ii)
Designated Sales Personnel	Schedule 5.2.4
Designated Personnel	Schedule 5.2.4
Different	7.2.5
Dispute	15.6
Distinct Indication	7.2.5
DOJ	14.2
Enforcing Party	8.3.3
Excess Cost Deferral Notice	7.7.2(a)
Excess Cost Opt In Amount	7.7.2(b)
Excess Cost Opt In Notice	7.7.2(b)
Excess Study Costs	7.7.2(a)
Excluded Entity	11.1.5(c)
Excluded Individual	11.1.5(c)
Execution Date	Preamble
Existing In-License Agreements	6.5.1
Expanded Indication CNS Product	7.4.1
Expanded Indication Peripheral Product	7.4.1
Falsified Medicine	8.7.1
Finance Working Group	7.7.7
Force Majeure Event	15.1
FTC	14.2
Fully Paid-Up	7.5.2(a)

Term	Section
Infringement Enforcement Action	8.3.2(a)
Initial CNS Phase III Trial Plan/Budget	3.2.1(b)(iv)
Initial CNS Phase III Trials	3.2.1(b)(iv)
Initial Transition Activities	3.3.3
JCC	2.3.1
JDC	2.2.1
JSC	2.1.1
Late Stage Competing Product	6.8.2(b)
Launch Window	5.2.4(c)
MAA	1.49
Major Market CNS Regulatory Filings	3.4.3(c)
Manufacture Working Group	4.5
Manufacturing Party	4.4
Manufacturing Transfer	4.1
Material Adverse CNS Program Effect	3.2.4(c)
New CNS Program Technology	6.5.2(a)(i)
New CNS Program Technology Terms	6.5.2(a)(i)(A)
New Peripheral Program Technology	6.5.2(b)(i)
Non-Breaching Party	13.2
Non-Enforcing Party	8.3.3
Non-Manufacturing Party	4.4
Party / Parties	Preamble
[***]	[***]
[***]	[***]
[***]	[***]
Payments	7.10.1

Fully Paid-Up License	7.5.3(a)
[***]	[***]
[***]	[***]
[***]	[***]
HSR Clearance Date	14.1
HSR Conditions	14.1
ICH	1.64
Indemnification Claim Notice	12.4
Indemnified Losses	12.1
Indemnified Party	12.4
Independent Third Party Lab	15.6.4
Indirect Taxes	7.11

Payments	7.10.1
PDE	Schedule 5.2.4
PDE Requirement	Schedule 5.2.4
Peripheral Milestone	7.3.1
Peripheral Milestone Payments	7.3.1
Peripheral Patient Samples	3.7
Pharmacovigilance Agreement	9.1
Phase 2 Notice	3.2.4(e)(i)
Phase 2 Update	3.2.4(e)(ii)

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Term	Section
Phase 3 Update	3.2.4(e)(iii)
Phase III Cohort	1.110
PIR	Schedule 5.2.4
[***]	[***]
[***]	[***]
Promotional Materials	″5.5
Proposing Party	″3.2.4(a)
Prosecuting Party	8.5.2
Publication Working Group	10.6.2
Quarterly Royalty Report	7.5.5
Regulatory Data	3.4.4
Royalty Term	7.5.3(b)(i)
Royalty Term Determining Product Patent	7.5.3(b)(ii)
Safety Study	1.143
Sanofi	Preamble
Sanofi Development Wind-Down Period	13.8.4(v)(A)
Sanofi Indemnitees	12.2
Sanofi Quality	3.2.3(a)(ii)
Sanofi Senior Officer	15.6.1
Sanofi Unblocking Know-How	13.8.1(c)

Term	Section
Sanofi Unblocking Patent Rights	13.8.1(c)
Senior Officers	15.6.1
Shared Cost Trials	1.143.1
Shared LTS Costs	1.143
[***]	[***]
SOPs	Schedule 5.2.4
Standard Cost	1.85.3
Supply and Quality Agreement	4.4
Technology Transfer Plan	3.3.1
Term	13.1
Terminated Area	13.3
Terminated Denali Products	13.8.1
Terminated Portion	13.8
Terminated Sanofi Products	13.8.4
Third Party Claims	12.1
Updated CNS Phase III Trial Plan/Budget	3.2.2(b)
Upfront Consideration	7.1
WHO ICD10	1.7
Working Group	2.7

ARTICLE 2
COLLABORATION MANAGEMENT

2.1 Joint Steering Committee.

2.1.1 Formation. As soon as practical, but no later than [***] after the Effective Date, the Parties shall establish a joint steering committee ("**JSC**"), which shall perform the functions set forth in **Section 2.1.2** (Specific Responsibilities) and oversee the conduct of the CNS Program and Peripheral Program in the Territory. The JSC shall consist of three (3) representatives from each of the Parties, unless otherwise agreed by the Parties in writing.

2.1.2 Specific Responsibilities. The JSC shall manage the implementation of this Agreement and oversee the Development and Commercialization of Compounds and Products in the Territory and, subject to **Section 2.4.5** (Joint Committee Decision Making), resolve certain matters that are not unanimously decided by the JDC or JCC. In particular, the JSC shall:

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(a) coordinate activities and facilitate communication of the Parties in connection with the Development and Commercialization of Compounds and Products included in the CNS Program and in the Peripheral Program, respectively;

(b) review and discuss the progress of activities in connection with the Development and Commercialization of Compounds and Products included in the CNS Program and in the Peripheral Program, respectively;

(c) coordinate and oversee the operation of the JDC, JCC and any other joint subcommittee established by JSC, including resolving any disputed matter of the JDC, JCC and other subcommittees in accordance with **Section 2.4.5** (Joint Committee Decision Making), and promote effective member participation in each such Committee's or subcommittee's operations;

(d) review and approve any amendment to the CNS Development Plan;

(e) review and approve any Additional CNS Development Proposal in accordance with **Section 3.2.4** (Additional CNS Program Development Activities);

(f) review and comment on the then-current Peripheral Development Plan, including any updates to the Peripheral Development Plan made by Sanofi in accordance with **Section 3.2.1(c)** (Content of Peripheral Development Plan);

(g) review the Global Commercialization Plan, including updates thereto made by Sanofi in accordance with **Section 5.3.3** (Amendments and Updates), and the progress of activities being conducted under the Global Commercialization Plan;

(h) oversee the execution of the Technology Transfer Plan;

(i) form Working Groups as needed to fulfill the obligations of the JSC under this Agreement, including a Finance Working Group unless Denali has exercised the Denali Royalty Option for all CNS Products pursuant to **Section 7.8** (Denali Royalty Option) with responsibilities as provided in **Section 7.7.7** (Financial Reporting Activities; Finance Working Group), [***], and a Manufacture Working Group with responsibility as provided in **Section 4.5** (Manufacture Working Group);

(j) oversee the Working Groups created by the JSC on all significant strategic issues that fall within the purview of each such Working Group;

(k) except with respect to matters within the responsibility of [***] or as otherwise agreed in writing by the Parties, resolve issues presented to the JSC by any Working Group established by such JSC;

(l) resolve issues presented to the JSC in accordance with this Agreement (including those matters outlined in **Section 2.4.5(b)(ii)**); and

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(m) perform such other functions as are set forth in this Agreement as the function of the JSC or as the Parties may otherwise mutually agree in writing.

2.2 Joint Development Committee.

2.2.1 Formation. As soon as practical, but no later than [***] after the Effective Date, the Parties shall establish a joint development committee ("**JDC**"). The JDC shall consist of three (3) representatives from each of the Parties, unless otherwise agreed by the Parties in writing.

2.2.2 Specific Responsibilities. The JDC shall oversee the Development of CNS Compounds and CNS Products in the Territory. In particular, the JDC shall:

(a) review and finalize, for the JSC's approval, any amendment to the then-current CNS Development Plan (including the then-current CNS Development Budget), and any Updated CNS Phase III Trial Plan/Budget), including any updates to such plan or budget in accordance with **Section 3.2.2** (Amendments and Updates);

(b) review and monitor the activities being conducted under the CNS Development Plan and the progress of such activities;

(c) with respect to the CNS Program, review and discuss the selection of clinical trial sites, clinical research organizations and other key Third Party Providers for Clinical Studies to be conducted in each country of the Cost Profit Sharing Countries included in the CNS Development Plan;

(d) with respect to the CNS Program, prepare and approve, the Parties' strategies related to funding for any investigator-initiated clinical trials for the Territory, including Clinical Studies involving a safety issue or the head-to-head comparison of a CNS Product with any other pharmaceutical agent;

(e) oversee and coordinate the preparation of the Transition Plan for approval by the Parties and the implementation of the Transition Plan;

(f) review and finalize, for the JSC's approval, any Additional CNS Development Proposal pertaining to the CNS Program; and

(g) perform such other functions as are set forth in this Agreement as the function of the JDC or as the Parties may otherwise mutually agree in writing.

2.3 Joint Commercialization Committee.

2.3.1 Formation. If Denali has exercised the Co-Commercialization Option, then no later than [***], the Parties shall establish a joint commercialization committee ("**JCC**"). The JCC shall consist of three (3) representatives from each of the Parties, unless otherwise agreed by the Parties in writing.

2.3.2 Specific Responsibilities. The JCC shall oversee and coordinate the Commercialization of CNS Compounds and CNS Products in the Territory. In particular, the JCC shall:

(a) review and finalize the Co-Commercialization Plan and Co-Commercialization Budget, and material amendments thereto, including any updates to such plan or budget in accordance with **Section 5.3.3** (Amendments and Updates);

(b) discuss, review and finalize reasonably in advance of the first Regulatory Approval for the first CNS Product, and annually thereafter, a non-binding [***] estimated sales forecast for the CNS Products;

(c) with respect to any CNS Product(s) and countries within the Co-Commercialization Territory with respect to which Denali has exercised the Co-Commercialization Option, prepare and approve, the Parties' strategies related to field-based medical education activities by either Party and grant-based medical education programs for such CNS Product(s) in each such country;

(d) monitor the competitive landscape for CNS Products in the Territory;

(e) discuss, review and finalize the Parties' strategies related to any marketing studies, epidemiological studies, modeling and pharmaco-economic studies, investigator-initiated clinical trials or post-marketing surveillance studies with respect to CNS Products in each country of the Co-Commercialization Territory;

(f) discuss pricing of CNS Products;

(g) review and approve the Detail position for CNS Products in the conduct of Co-Commercialization Activities;

(h) implement a process for reviewing and approving (i) Promotional Materials and (ii) training materials and programs for sales representatives, in each case (i) and (ii), that are intended for use with Co-Commercialization Products in applicable Co-Commercialization Countries to the extent to which Denali has exercised its Co-Commercialization Option; and

(i) perform such other functions as are set forth in this Agreement as the function of the JCC or as the Parties may otherwise mutually agree in writing.

2.4 General Provisions Applicable to Joint Committees.

2.4.1 Meetings and Minutes. The JSC shall meet at least semi-annually, or as otherwise agreed to by the JSC. The JDC shall meet at least once per Calendar Quarter, or as otherwise agreed to by the JDC. Beginning after the formation of the JCC, the JCC shall meet at least once per Calendar Quarter, or as otherwise agreed to by the JCC. Meetings of each Joint Committee may be conducted by telephone, video-conference, or in-person as determined by such Joint Committee. In-person meetings of each Joint Committee, unless otherwise agreed, shall

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alternate between Denali's offices and Sanofi's offices. Regularly scheduled meetings of each Joint Committee may be called by either Party on no less than [***] notice, or such shorter time period as agreed by the members. Each Party shall make all proposals for agenda items for regularly scheduled meetings of a Joint Committee, and shall provide all appropriate information with respect to such proposed items, to the Alliance Managers at least [***] in advance of the applicable meeting, or such shorter time period as agreed by the Parties. Each Party may also call a special meeting of a Joint Committee to resolve particular matters requested by such Party, on no less than [***] notice (or such shorter time period as may be appropriate under the circumstances, but in no event less than [***] notice). In the case of a special meeting of a Joint Committee called by a Party, the proposed agenda items and appropriate information with respect to such proposed items shall be provided together with the notice calling for such special meeting to the other Party. Draft minutes of the meetings of any Joint Committee will be generated and circulated to its members within [***] following the meeting. The responsibility for generating and circulating such minutes will alternate between the Alliance Managers (or their designees). The Joint Committees will use diligence to review and finalize the minutes within [***] after their circulation and, in all circumstances, no later than the next meeting of the same Joint Committee.

2.4.2 Chairpersons. Unless Denali exercises the Denali Royalty Option with respect to all CNS Products included in the CNS Program, the Joint Committees shall each have co-chairpersons that each of Denali and Sanofi select from their respective representatives. Each Party may change any of its designated chairpersons from time to time upon written notice to the other Party. In the event Denali exercises the Denali Royalty Option with respect to all CNS Products included in the CNS Program, the chairperson for the JSC shall be appointed by Sanofi.

2.4.3 Procedural Rules. Each Joint Committee shall have the right to adopt such standing rules as shall be necessary for its work, to the extent that such rules are not inconsistent with this Agreement; *provided* that such rules shall not be subject to a deciding vote of either Party having final decision-making authority for such committee. At least [***] representatives from each Party on each Joint Committee shall have the requisite seniority to make decisions on behalf of the relevant Party with respect to the issues falling within the decision-making authority of the relevant Joint Committee. A quorum of the Joint Committee shall exist whenever there is present at a meeting at least [***] representative appointed by each Party with the requisite seniority to make decisions described in the second sentence of this **Section 2.4.3**. From time to time, each Party may substitute one (1) (or more, if applicable) of its representatives to a particular Joint Committee by advance, written notice to the other Party, *provided* that the criteria in the second sentence of this **Section 2.4.3** shall continue to be satisfied.

2.4.4 Meeting Attendance by Non-Members. Employees or other representatives of either Party (or a Party's Affiliate) who are not appointed members of a Joint Committee may attend meetings of such Joint Committee; *provided* that the Party wishing such persons to participate in a meeting has provided reasonable advance notice to the other Party. Non-employees may only attend meetings of a Joint Committee (a) if such non-employee is bound by written obligations of confidentiality and non-disclosure substantially equivalent to those set forth in **Article 10** (Confidentiality and Non-Disclosure) or is otherwise bound by professional ethical

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obligations, and (b) with the prior written approval of the other Party (such approval not to be unreasonably withheld, delayed or conditioned).

2.4.5 Joint Committee Decision Making.

(a) **Voting**. Except as set forth in **Section 2.4.5(b)** (Final Decision-Making Authority), the decisions of each Joint Committee shall be by unanimous agreement. Each Party shall have a single vote on a matter to be decided by the applicable Joint Committee irrespective of the number of representatives of such Party in attendance at the applicable Joint Committee meeting. Decisions of a Joint Committee will be documented in the relevant final approved meeting minutes or, should a decision be made outside of a meeting forum, such decision may also be made by a written resolution unanimously agreed by the Parties; it being understood that such unanimous written agreement may be provided by email.

(b) **Final Decision-Making Authority**. If the JDC or JCC does not reach unanimous agreement on an issue for decision by the JDC or JCC within [***] after the meeting at which such issue was first presented for decision by the JDC or JCC, as the case may be, despite good faith efforts to do so, then Sanofi shall have final decision-making authority under this **Section 2.4.5(b)**, except as set forth below solely with respect to the CNS Program:

(i) [***] will have final decision making authority over (A) [***]; and (C) [***];

(ii) [***], in each case, shall be escalated to [***] in the event of a disagreement among [***], as applicable, and then, if there is a disagreement among [***], such matter shall be escalated to [***]; *provided* that, except as set forth in the foregoing clause (i) above, [***]; and

(iii) Additional CNS Development Activities shall be governed by **Section 3.2.4** (Additional CNS Development Program Activities) (including the restrictions and limitations set forth therein).

The decision of the applicable Party's representative on a Joint Committee with respect to an issue for which such Party has the deciding vote shall become the decision of the applicable Joint Committee.

2.4.6 Limitations on Authority. Each Party shall retain the rights, powers, and discretion granted to it under this Agreement and no such rights, powers, or discretion shall be delegated to or vested in a Joint Committee unless such delegation or vesting of rights is expressly provided for in this Agreement or the Parties expressly so agree in writing. Except for amendments and modifications to the Development Plans, Commercialization Plans, and Co-Commercialization Plans in accordance with this **Article 2** (Collaboration Management), **Section 3.2.2** (Amendments and Updates), **Section 3.2.4(b)** (Inclusion of Additional CNS Development Activities in the CNS Development Plan), **Section 3.2.4(e)(v)** (Additional CNS Development Opt-In Notice) and **Section 5.3.3** (Amendments and Updates), no Joint Committee shall have the power to, and no deciding vote of a Party shall, amend, modify, or waive compliance with this Agreement, which

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may only be amended or modified as provided in **Section 15.8** (Entire Agreement; Amendments) or compliance with which may only be waived as provided in **Section 15.11** (Waiver and Non-Exclusion of Remedies). No decision of any Joint Committee (including by a Party in the exercise of its deciding vote in accordance with **Section 2.4.5** (Joint Committee Decision Making) shall (a) finally determine any interpretation of this Agreement or the Parties rights or obligations hereunder, or (b) conflict with any terms and conditions of this Agreement, nor be in contravention of Applicable Law in any material respect. For the avoidance of doubt, disputes arising between the Parties in connection with or relating to this Agreement, or any document or instrument delivered in connection herewith, that are outside of the decision-making authority of the Joint Committees and not within a Party's sole decision-making authority hereunder, shall be resolved pursuant to **Section 15.6.3** (ADR).

2.4.7 [***]. [***] in no event shall [***].

2.5 Discontinuation of Joint Committees. Each Joint Committee shall continue to exist until the first to occur of: (a) the Parties mutually agreeing to disband the Joint Committee; (b) Denali providing to Sanofi written notice of its intention to disband and no longer participate in such Joint Committee; or (c) (i) with respect to the JDC, the cessation of Development activities under the CNS Development Plan, *provided* that the JDC shall resume upon commencement of any such Development activities; and (ii) with respect to the JCC, (A) the cessation of Co-Commercialization Activities under the Co-Commercialization Plan (*provided* that the JCC shall resume upon commencement of any such Co-Commercialization Activities), or (B) at Sanofi's election in accordance with **Section 6.8.2(b)** (Change in Control Competing Product), to the extent applicable. Notwithstanding anything herein to the contrary, once one or more Joint Committees have been disbanded, such disbanded Joint Committee and all Working Groups appointed by such Joint Committee shall be terminated and thereafter (x) any requirement of a Party to provide Information or other materials to such Joint Committee or its Working Group(s) shall be deemed a requirement to provide such Information or other materials to the other Party directly, and (y) any matters previously delegated to the Joint Committee for decision making may be decided by Sanofi, subject to the procedures set out in **Section 2.4.5(b)(ii)** to the extent applicable.

2.6 Alliance Manager. Within [***] after the Effective Date, each Party shall appoint an individual to act as a single point of contact between the Parties to facilitate the effective exchange of information between the Parties, discuss the performance of the Agreement, and ensure that the Parties' activities are conducted in accordance with this Agreement (each, an "**Alliance Manager**"). Each Party may replace its Alliance Manager at any time by notice in writing to the other Party. The Alliance Managers (or their designees) will be responsible for coordinating the Joint Committees and any Working Groups by organizing their meetings, helping to develop the agendas for the meetings, and drafting and finalizing meeting minutes. Each Alliance Manager will be charged with creating and maintaining effective communication within and among the Parties. Each Alliance Manager may have additional responsibilities as agreed between Parties.

2.7 Working Groups. From time to time, a Joint Committee may establish and delegate duties to sub-committees or directed teams (each, a "**Working Group**") to oversee particular projects or activities [***].

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2.8 Expenses. Each Party shall be responsible for all travel and related costs and expenses for its representatives and, if applicable, its (or any of its Affiliates') other personnel to attend meetings of, and otherwise participate in, a Joint Committee or other Working Group.

ARTICLE 3
DEVELOPMENT AND REGULATORY ACTIVITIES

3.1 RIPK1 Inhibitor and CNS Penetrance Determinations. [***], as the case may be, [***], the Parties shall [***]. In any event, [***], the Parties shall [***].

3.2 Development Plan and Activities.

3.2.1 Development Plans.

(a) **Initial Development Plans**. An Initial CNS Development Plan and CNS Development Budget, as well as an Initial Peripheral Development Plan are attached to this Agreement as **Schedule 1.73, Schedule 1.74** and **Schedule 1.75**, respectively.

(b) **Content of CNS Development Plan and CNS Development Budget**.

(i) The CNS Development Plan shall: (A) outline those Denali CNS Development Activities and Sanofi CNS Development Activities to be conducted by the applicable Party, including descriptions, in reasonable detail, of (I) Clinical Studies to be conducted for each applicable CNS Product, (II) any activities for the development of [***], in each case for the applicable CNS Products, [***], and (III) the contemplated Regulatory Approval(s) such Denali CNS Development Activities and Sanofi CNS Development Activities are intended to support; (B) include a timeline for the Denali CNS Development Activities and the Sanofi CNS Development Activities; and (C) state the estimated number of FTEs of each Party or its Affiliates to be allocated to the relevant Development activities for any Phase III Trials for a CNS Product.

(ii) The CNS Development Plan shall also include the budgeted amounts of Development Costs that the Parties' estimate in good faith (which shall reflect the relevant Development Lead's internal budgeting projections) will be incurred for any Phase III Trial for a CNS Product, including any Shared LTS Costs for any associated Safety Study, to be undertaken in accordance with such plan (the Initial CNS Development Budget and any such amended budget included in the CNS Development Plan from time to time in accordance with the terms of this Agreement, the "**CNS Development Budget**").

(iii) The CNS Development Plan and CNS Development Budget shall be reasonably detailed with respect to the contemplated Development and Manufacturing activities, and estimated FTE Costs, Out-of-Pocket Costs and Manufacturing Costs included in Development Costs for any Phase III Trial for a CNS Product (including with respect to Shared LTS Costs), broken down by Party and by Calendar Quarter, and in the case of each Phase III Trial included in the then-current CNS Development Plan, by Phase III Trial, for the first Calendar Year (or part thereof) and shall also outline, by Calendar Year for the next [***], the then-current estimate of Development and

Manufacturing activities (including estimated associated FTE Costs and Out-of-Pocket Costs and Manufacturing Costs included in Development Costs for any Phase III Trial for a CNS Product, including any Shared LTS Costs, in each case, broken down by Phase III Trial). In the event Denali has exercised the Denali Royalty Option pursuant to **Section 7.8** (Denali Royalty Option) for all CNS Products included in the CNS Program, the CNS Development Plan shall be limited to [***].

(iv) Notwithstanding the foregoing provisions in this **Section 3.2.1(b)**, the Parties acknowledge and agree that: (A) the Initial CNS Development Plan and Initial CNS Development Budget cover a longer period of time than [***] years; (B) the Initial CNS Development Plan outlines a total of [***], including the Shared LTS Costs, comprising [***] (collectively, such Phase III Trials and other Clinical Studies, the "**Initial CNS Phase III Trials**"); and (C) the Initial CNS Development Budget outlines the Development Costs estimated for each of the Initial CNS Phase III Trials (such portion of the Initial CNS Development Budget for each Initial CNS Phase III Trial, an "**Initial CNS Phase III Trial Plan/Budget**") excluding the [***], in each case, that may be used in each Initial CNS Phase III Trial.

(c) **Content of Peripheral Development Plan**. The Peripheral Development Plan shall be a high-level plan that outlines the material activities to be conducted by or under the authority of Sanofi with respect to Peripheral Compounds and Peripheral Products, which plan shall include at least those Development activities to be conducted in order to obtain Regulatory Approval for [***] to the extent such activities are necessary to meet Sanofi's obligations under **Section 3.2.3(a)**.

3.2.2 Amendments and Updates.

(a) **General**. The JDC shall review the CNS Development Plans on a regular basis, and in no event less frequently than once each [***]. Either Party, through its representatives on the JDC, may propose amendments to, and comment upon, the CNS Development Plan (including the CNS Development Budget or Updated CNS Phase III Trial Plan/Budget) from time to time. In any event, an updated CNS Development Plan shall be provided by the JDC to the JSC (and, with respect to each updated CNS Development Plan, approved by the JSC as required) no later than December 1 of each Calendar Year. [***].

(b) **CNS Phase III Trial Updates**. Without limiting **Section 3.2.2(a)** (General), no later than [***] prior to the first Calendar Quarter in which the Initiation of each Phase III Trial for a CNS Product that is included in the CNS Development Plan is scheduled to occur under the CNS Development Plan, Sanofi shall update the applicable portions of the CNS Development Plan and CNS Development Budget to reflect the most-current planned activities pertaining to such Phase III Trial and any associated Safety Study and the budgeted amounts in reasonable detail of the FTE Costs, Out-of-Pocket Costs and Manufacturing Costs estimated in good faith (which shall reflect Sanofi's internal budgeting projections) to be incurred for such Initial CNS Phase III Trial, including any Active Comparator Costs estimated in good faith for such Phase III Trial and any FTE Costs, Out-of-Pocket Costs and Manufacturing Costs incurred prior to such date with respect to such Initial CNS Phase III Trial (such updated portion of the CNS Development Budget, an "**Updated CNS Phase III Trial Plan/Budget**").

3.2.3 Development Activities.

(a) **Efforts**. Sanofi shall use Commercially Reasonable Efforts to seek and obtain Regulatory Approval for (x) [***], and (y) [***]. In addition, and without limiting the foregoing, the following shall apply:

(i) each Party shall use Commercially Reasonable Efforts to perform the Development activities allocated to it under the then-current CNS Development Plan;

(ii) Sanofi shall [***], *provided* that [***]; or [***]; *provided* that, in each case, [***];

(iii) Sanofi [***];

(iv) Sanofi [***]; and

(v) Sanofi [***].

(vi) Notwithstanding the foregoing, with respect to the time periods set forth in the foregoing clauses (iv) and (v), each such time period shall [***].

(vii) [***].

(viii) [***].

(b) **Allocation of Peripheral Program Activities and Costs**. Sanofi shall be responsible for, and bear the cost of, the planning and conduct of all Development activities with respect to the Peripheral Program in a manner consistent with the then-current Peripheral Development Plan; *provided* that Denali shall provide reasonable assistance and support as set forth in the Technology Transfer Plan, and otherwise as mutually agreed by the Parties.

(c) **Development Leads; Additional CNS Program Activities**.

(i) **Development Leads.** For the CNS Program, Denali shall be the Development Lead for, and shall be primarily responsible for the planning and conduct of, the Denali CNS Development Activities, and Sanofi shall be the Development Lead for, and shall be primarily responsible for the planning and conduct of, the Sanofi CNS Development, in each case, in a manner consistent with the then-current CNS Development Plan; *provided, however*, that Denali shall also be primarily responsible for conducting the Phase Ib Trial for DNL747 for ALS as outlined in the Initial CNS Development Plan pursuant to a protocol for such Phase Ib Trial mutually agreed by the Parties, and Sanofi shall reimburse Denali for its Development Costs incurred for such Phase Ib Trial. For the avoidance of doubt, notwithstanding the initiation of Sanofi CNS Development Activities for a particular CNS Product, Denali will continue to be Development Lead for any additional Denali CNS Development Activities with respect to [***], unless otherwise agreed between the Parties.

(ii) **Role of Non-Development Lead.** In addition to any activities that the Parties agree the Non-Development Lead may conduct within the CNS Program, the Non-Development Lead shall have the right to have one (1) or more of its employees attend, and participate in, all global advisory board meetings and other meetings with key opinion leaders regarding the CNS Program, or any CNS Compounds or CNS Products.

(iii) **Costs of Certain Additional Activities.** If the Parties mutually agree, Denali may conduct certain pre-clinical and non-clinical activities (including non-clinical toxicology studies and activities related to the discovery or development of biomarkers), Clinical Studies or other Development activities pertaining to the CNS Program, in each case, that are not Denali CNS Development Activities; and Sanofi shall reimburse Denali for its Development Costs incurred in the performance of any such activities that are not Denali CNS Development Activities, and Denali shall provide Sanofi with an estimated budget for such activities in advance (which budget shall be prepared by Denali in good faith and consistent with its internal budgeting for other products). Otherwise, all FTE Costs and Out-of-Pocket Costs that the Parties incur or accrue in connection with the Development of CNS Compounds and CNS Products under the CNS Development Plan shall be borne or shared in accordance with **Section 7.7** (Cost Profit Sharing) subject to **Section 7.8** (Denali Royalty Option).

(d) **Transition of Development Lead for the CNS Program**. Reasonably in advance of the Initiation of Sanofi CNS Development Activities for a particular CNS Product, the JDC will prepare a Transition Plan to be approved by the Parties for the transfer of the Development Lead with respect to such CNS Product from Denali to Sanofi.

(e) **CNS Program Development Reports**. For the CNS Program, each Party shall report on the Development activities such Party has performed (or caused to be performed) under the CNS Program in accordance with the procedures established by the JDC. The JDC shall evaluate the work performed in relation to the goals of the CNS Development Plan. The Parties shall provide such other Information as may be reasonably requested by the JDC with respect to such Development activities for the CNS Program.

(f) **Performance of Development Activities**. Each Party shall perform any and all of its Development activities with respect to the Programs in accordance with the applicable Development Plan, in good scientific manner and in compliance with all Applicable Law, including applicable national and international (*e.g.*, ICH, GCP, GLP, and GMP guidelines), informed consent and institutional review board regulations, current standards for pharmacovigilance practice, and all applicable requirements relating to the protection of human subjects.

3.2.4 Additional CNS Program Development Activities. Each Party shall be permitted to undertake Clinical Studies [***] (any such activities, the "**Additional CNS Development Activities**", and any such Clinical Study, the "**Additional CNS Development Study**"); *provided* that such Party complies with the provisions of this **Section 3.2.4**.

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(a) **Additional CNS Development Proposals**. If a Party (such Party, the "**Proposing Party**") desires to undertake Additional CNS Development Activities, such Party shall submit to the JDC a proposal for the addition of such Additional CNS Development Activities to the CNS Development Plan that includes a proposed work plan, timeline and budget for such Additional CNS Development Activities ("**Additional CNS Development Proposal**"). The Additional CNS Development Proposal shall be prepared in a similar scope and format of the CNS Development Plan. The Proposing Party shall provide the JDC with any additional Information related to the Additional CNS Development Proposal reasonably requested by the JDC.

(b) **Inclusion of Additional CNS Development Activities in the CNS Development Plan**. The JDC shall review and decide on such Additional CNS Development Proposal within [***] after its receipt of such Additional CNS Development Proposal; *provided* that such time shall be extended if the Proposing Party has not provided all available Information reasonably requested by the JDC during such [***] period. If the JDC approves an Additional CNS Development Proposal, such Additional CNS Development Proposal shall be submitted promptly to the JSC for review. If the JSC approves an Additional CNS Development Proposal, the CNS Development Plan shall be deemed to be amended to include the Additional CNS Development Activities and associated budget upon approval of such Additional CNS Development Proposal by the JSC. For the sake of clarity, all Development Costs incurred thereafter by the Parties in performing such Additional CNS Development Activities shall be treated as Shared Development Costs unless and until the Co-Funding End Date occurs with respect to such CNS Product that is the subject of such Additional CNS Development Activities. If the JSC does not approve the Additional CNS Development Proposal, such proposal shall not be deemed to be part of the CNS Development Plan and the provisions of **Section 3.2.4(c)** (Objection by the Other Party) to **Section 3.2.4(e)** (Opt-In for Additional CNS Development Activities) shall apply.

(c) **Objection by the Other Party**. If the JSC does not timely approve an Additional CNS Development Proposal within the time periods set forth in **Section 3.2.4(b)** (Inclusion of Additional CNS Development Activities in the CNS Development Plan), the Proposing Party shall be entitled to conduct the corresponding Additional CNS Development Activities at its own cost and notwithstanding the other Party's objection (such other Party, the "**Declining Party**"), except that, if Denali is the Proposing Party, Denali will not be entitled to conduct such Additional CNS Development Activities if [***]. Upon receiving notice from [***] (which notice shall provide in reasonable detail the basis of such determination), [***].

(d) **Performance of Additional CNS Development Activities**. If the Proposing Party conducts the relevant Additional CNS Development Activities at its cost and notwithstanding a decision by the JSC not to approve the Additional CNS Development Proposal, but not in contravention of **Section 3.2.4(c)** (Objection by the Other Party), the following shall apply until the Proposing Party's receipt of an Additional CNS Development Opt-In Notice for such Additional CNS Development activities:

(i) the CNS Product that is the subject of Additional CNS Development Activities shall continue to be a CNS Product for all purposes of this Agreement, *provided* that the milestones set forth in **Section 7.2** (CNS Program Milestones) and **Section 7.3** (Peripheral Program Milestones), as the case may be, shall not become payable due to any such Additional CNS Development Activities unless and until the earlier of (A) the issuance of an Additional CNS Development Opt-In Notice by the Declining Party with respect to such activities, or (B) the applicable Regulatory Authority in a Major Market accepting an Additional Regulatory Approval Application for substantive review in accordance with **Section 3.2.4(e)(v)** (Additional CNS Development Opt-In Notice), in which case (with respect to (A) and (B)) any applicable milestone events shall be deemed achieved as of the date such provisos ((A) or (B)) are satisfied.

(ii) the Proposing Party shall be the Development Lead and Regulatory Lead (except with respect to the preparation of any applications or submissions, including New Drug Applications, for Regulatory Approval, which shall remain Sanofi's sole responsibility in accordance with **Section 3.2.4(e)(iv)** (Application for Regulatory Approval)) with respect to such Additional CNS Development Activities, until the Proposing Party's receipt of an Additional CNS Development Opt-In Notice for such Additional CNS Development Activities (or, if applicable, an Additional CNS Development Opt-In Notice is deemed to have been issued pursuant to **Section 3.2.4(e)(iv)** (Application for Regulatory Approval), after which the provisions of **Section 3.2.3** (Development Activities) shall apply.

(iii) In the event the Proposing Party is not then-responsible for Manufacturing the applicable CNS Compound or CNS Product and will not Manufacture (or have Manufactured by a Third Party) quantities of the applicable CNS Compound or CNS Product to support the Additional Development Activities, then, subject to **Section 4.4** (Supply Agreements), [***].

(iv) The Proposing Party shall initially bear all costs associated with the Additional CNS Development Activities it undertakes and such costs shall not be taken into account as Shared Development Costs or as Allowable Expenses.

(v) Except as expressly set forth in this Section 3.2.4(d), the conduct of the Additional CNS Development Activities will be subject to all terms and conditions of this Agreement relating to Development of CNS Products. The Declining Party shall have the right to use, at no additional cost, any safety data arising from the Additional CNS Development Activities in the performance of its obligations and the exercise of its rights under this Agreement in accordance with the licenses and rights granted under Article 6 (License Grants; Exclusivity).

(vi) Additional CNS Development Activities undertaken by the Proposing Party shall be subject to the oversight of the JDC and the Declining Party shall have the right to provide comments thereon, which the Proposing Party shall reasonably consider; [***]. At each meeting of the JDC, the Proposing Party shall report its progress with regard to the Additional CNS Development Activities in the same manner as the Parties provide reports to the JDC with respect to activities covered by the CNS Development Plan, including providing formal written reports of the results related to the Additional CNS Development Activities, as well as the actual costs incurred by the Proposing Party, along with estimated future budgets.

(e) **Opt-In for Additional CNS Development Activities**.

(i) **Initiation of a Phase 2 Trial.** No less than [***], the Proposing Party shall furnish to the JDC and the Declining Party, the protocol for such Clinical Study, the results of any preceding and related Phase I Trials and the Additional CNS Development Costs incurred to date by the Proposing Party ("Phase 2 Notice"). The Proposing Party shall also provide the JDC with any other Information related to the Additional CNS Development Activities which is reasonably requested by the JDC and available to the Proposing Party. If, within [***] of the Declining Party's receipt of the Phase 2 Notice, the Declining Party notifies the JDC and the Proposing Party in writing that it desires to include the Additional CNS Development Activities into the CNS Development Plan (such notice, whenever given in accordance with this Section 3.2.4(e) (Opt-In for Additional CNS Development Activities), an "Additional CNS Development Opt-In Notice"): (1) the Declining Party shall, subject to the review rights set forth in Section 7.7.3(b) (Expense Review) and to the extent applicable, pay to the Proposing Party an amount equal to that portion of the Additional CNS Development Costs identified in the Phase 2 Notice that would have been borne by the Declining Party if such Additional CNS Development Activities had been included in the CNS Development Plan [***], which amount shall be due within [***] of invoicing by the Proposing Party; and (2) the terms of Section 3.2.4(e)(v) (Additional CNS Development Opt-In Notice) shall apply.

(ii) **Completion of a Phase 2 Trial.** Within [***], the Proposing Party shall furnish to the JDC and the Declining Party a written report of the results of such Clinical Study and the Additional CNS Development Costs incurred by the Proposing Party since the Phase 2 Notice ("Phase 2 Update"). The Proposing Party shall also provide the JDC with any other Information related to the Additional CNS Development Activities which is reasonably requested by the JDC and available to the Proposing Party. If, within [***] of the Declining Party's receipt of the Phase 2 Update, the Declining Party provides an Additional CNS Development Opt-In Notice: (1) the Declining Party shall, subject to the review rights set forth in to Section 7.7.3(b) (Expense Review) and to the extent applicable, pay to the Proposing Party an amount equal to that portion of the Additional CNS Development Costs identified in the Phase 2 Notice and the Phase 2 Update that would have been borne by the Declining Party if such Additional CNS Development Activities had been included in the CNS Development Plan [***]; which amount shall be due within [***] of invoicing by the Proposing Party and (2) the terms of Section 3.2.4(e)(v) (Additional CNS Development Opt-In Notice) shall apply.

(iii) **Completion of Phase 3 Trial**. In the event that the Declining Party has not submitted the Additional CNS Development Opt-In Notice in accordance with Section 3.2.4(e)(ii) (Completion of a Phase 2 Trial), then within [***], the Proposing Party shall furnish to the JDC and the Declining Party a written report of the results of such Clinical Study and the Additional CNS Development Costs incurred by the Proposing Party since the Phase 2 Update ("Phase 3 Update"). The Proposing Party shall also provide the JDC with any other Information related to the Additional CNS Development Activities which is reasonably requested by the JDC and available to the Proposing Party. If, within [***] of the Declining Party's receipt of the Phase 3 Update, the Declining Party submits an Additional CNS Development Opt-In Notice to the JDC and Proposing Party: (1) the Declining Party shall, subject to the review rights set forth

in to Section 7.7.3(b) (Expense Review), pay to the Proposing Party an amount equal to the total of (x) that portion of the Additional CNS Development Costs identified in the Phase 2 Notice and Phase 2 Update that would have been borne by the Declining Party if such Additional CNS Development Activities had been included in the CNS Development Plan multiplied by the applicable Opt-in Premium Rate, [***]; which amount shall be due within [***] of invoicing by the Proposing Party; and (2) the terms of Section 3.2.4(e)(v) (Additional CNS Development Opt-In Notice) shall apply.

(iv) **Application for Regulatory Approval**. If the Declining Party decides not to submit an Additional CNS Development Opt-In Notice to the JDC and the Proposing Party following receipt of the Phase 3 Update and in the timeframe specified above in clause (iii), then the JSC shall, within a reasonable time thereafter, discuss whether to seek any Regulatory Approvals based on the applicable Additional CNS Development Activities, *provided*, [***]. If [***] ("**Additional Activity Regulatory Approval Application**"), then: (x) [***] (within no less than [***]) of the filing of such Additional Activity Regulatory Approval Application and shall also deliver written notice to [***] within [***] after such Additional Activity Regulatory Approval Application is accepted for substantive review by the applicable Regulatory Authority (which notice shall also be deemed to be an "Additional CNS Development Opt-In Notice" for the purposes of this **Section 3.2.4(e)** (Opt-In for Additional CNS Development Activities) even if [***] was the Proposing Party with respect to the relevant Additional CNS Development Study(ies)), (y) the terms of **Section 3.2.4(e)(v)** (Additional CNS Development Opt-In Notice) shall apply, and (z) (i) if the Additional Development Activities were conducted by Denali, Sanofi shall pay Denali an amount equal to the total of (1) that portion of the Additional CNS Development Costs identified in the Phase 2 Notice and Phase 2 Update that would have been borne by Sanofi if such Additional CNS Development Activities had been included in the CNS Development Plan [***], plus (2) the Additional CNS Development Costs identified in the Phase 3 Update for the relevant Additional CNS Development Study(ies) [***]; which amount shall be due to Denali within [***] of invoicing by Denali; and (ii) if the Additional Development Activities were conducted by Sanofi and Sanofi's Drug Approval Application is seeking Regulatory Approval in a Major Market, then Denali shall have the right to elect, by written notice to Sanofi during the applicable time period specified in clauses (xx) or (yy) in the following sentence, either (A) to pay Sanofi an amount equal to the total Additional CNS Development Costs identified in the Phase 3 Update for the relevant Additional CNS Development Study(ies) [***], which amount shall be due to Sanofi within [***] of invoicing by Sanofi following the Additional Activity Regulatory Approval Application being accepted for substantive review by the applicable Regulatory Authority; or (B) to exercise the Denali Royalty Option pursuant to **Section 7.8** (Denali Royalty Option) with respect to the CNS Product to which such Additional Activity Regulatory Approval Application relates, in which case Denali would have no obligation to pay Sanofi any of the applicable Additional CNS Development Costs, and Sanofi would not have the right to offset or credit such amounts against any payments to Denali under this Agreement. Denali shall only be entitled to make the election provided in foregoing clauses (A) and (B) of the preceding sentence during the following time periods: (xx) [***]; and (yy) [***]. [***].

(v) **Additional CNS Development Opt-In Notice**. Immediately upon the Proposing Party's receipt of a timely Additional CNS Development Opt-In

Notice: (i) the Additional CNS Development Activities (if any) for such CNS Product and the applicable Indication of the Additional CNS Development Activities shall be deemed to be included in the CNS Development Plan; (ii) the then-current plan and budget for such Additional CNS Development Activities shall be deemed to be included within and part of the CNS Development Plan, and shall control with respect to such Additional CNS Development Activities unless and until an amendment to the CNS Development Plan providing for a different or modified plan and budget is approved by the JSC in accordance with **Section 3.2.2** (Amendments and Updates); (iii) all Development Costs incurred thereafter in connection with such Additional CNS Development Activities shall be treated as Shared Development Costs and borne or shared by the Parties in accordance with **Section 7.7** (Cost Profit Sharing) unless and until the Co-Funding End Date occurs after Denali exercises the Denali Royalty Option pursuant to **Section 7.8** (Denali Royalty Option) with respect to the CNS Product that is the subject of the applicable Additional Development Activities; and (iv) to the extent the Co-Commercialization Plan or Global Commercialization Plan for such CNS Product then-exists and the Phase 3 Update has occurred, the JCC will update such Co-Commercialization Plan and Global Commercialization Plan in accordance with **Section 5.3.3** (Amendments and Updates) to address Commercialization of such CNS Product for the applicable Indication in any country for which Regulatory Approval is obtained.

(vi) **Sanofi Diligence**. Sanofi's obligations to use Commercially Reasonable Efforts to seek and obtain Regulatory Approval for any Product under **Section 3.2.3(a)** (Efforts) [***].

(vii) **Denali Royalty Option**. Notwithstanding the foregoing, in the event Denali exercises the Denali Royalty Option with respect to a particular CNS Product, Denali shall not be permitted to undertake any Additional CNS Development Activities pursuant to this **Section 3.2.4** (Additional CNS Program Development Activities) with respect to such CNS Product, and Sanofi shall have the right to conduct Additional CNS Development Activities with respect to such CNS Product by amending the applicable CNS Development Plan, and this **Section 3.2.4** (Additional CNS Program Development Activities) will not apply to such activities by Sanofi after the Co-Funding Date with respect to such CNS Product.

3.3 Disclosure of Technology for Development Purposes.

3.3.1 Technology Transfer Plan and Procedure. Promptly but no later than [***] after the Effective Date, pursuant to a technology transfer plan attached hereto in **Schedule 3.3.1** ("**Technology Transfer Plan**"), Denali shall disclose or otherwise make available to Sanofi the Regulatory Documentation and Denali Know-How existing as of the Effective Date and listed in the Technology Transfer Plan or otherwise reasonably requested and specifically identified by Sanofi. The JDC shall establish a process pursuant to which each Party shall disclose and make available to the other Party: Regulatory Documentation, Denali Know-How or Sanofi Know-How (including, in each case, any Joint Program Know-How), and other Information claimed or Covered by any Denali Patent, Sanofi Patent or Joint Program Patent or otherwise relating, directly or indirectly, to Compounds and Products, in each case to the extent Controlled by such Party or any of its Affiliates and reasonably necessary or reasonably useful for the other Party to Develop, Manufacture, or Commercialize such Compounds and Products in the Territory in

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accordance with the terms of this Agreement to the extent such items have not previously been provided to the other Party, *provided*, *however*, that, notwithstanding the foregoing, promptly following the Effective Date, Denali will provide Sanofi with an electronic media storage device (such as a portable storage drive, DVD or CD-ROM) containing an electronic copy of the data that was made available to Sanofi by Denali in an electronic data room prior to the Effective Date. To the extent not specified in the Technology Transfer Plan, the Parties shall cooperate and reasonably agree upon formats and procedures to facilitate the orderly and efficient exchanges of Regulatory Documentation, Information, or inventions contemplated under this **Section 3.3.1**.

3.3.2 Cooperation. Each Party shall, to the extent requested by the other Party, provide such other Party with all reasonable assistance required in order to transfer to the other Party the Regulatory Documentation, Denali Know-How and Sanofi Know-How (including, in each case, any Joint Program Know-How), and other Information required to be provided pursuant to **Section 3.3.1** (Technology Transfer Plan and Procedure), in each case in a timely manner, and shall assist the other Party with respect to the Exploitation of any Compound and any Products in accordance with the terms of this Agreement; *provided* that such Party's requirement to provide the other Party any tangible items, including any documentation, shall be limited to those items then-existing and Controlled by such Party or any of its Affiliates at the time of such request by the other Party; *provided*, *further*, that in the event Denali exercises the Denali Royalty Option for any given CNS Product included in the CNS Program in a Cost Profit Sharing Country, Sanofi shall not be required to make such Regulatory Documentation, Sanofi Know-How (including any Joint Program Know-How) or other Information available to Denali for such Cost Profit Sharing Opt Out Product applicable solely to the corresponding Cost Profit Sharing Opt Out Country(ies). Without limiting the foregoing, if visits of a Party's representatives to the other Party's facilities are reasonably requested by the other Party for purposes of transferring such Regulatory Documentation, Denali Know-How, Sanofi Know-How, Joint Program Know-How or other Information Controlled by a Party to the other Party or for purposes of the other Party acquiring expertise on the practical application of such Information or assisting on issues arising during such Exploitation, such Party shall use Commercially Reasonable Efforts to [***].

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3.3.3 Initial Transition Activities. The Technology Transfer Plan shall include certain pre-clinical and non-clinical activities to be conducted by Denali and activities with respect to the Manufacture of certain Licensed Compounds and Licensed Products, as further described in **Schedule 3.3.3** ("**Initial Transition Activities**"). Sanofi shall reimburse Denali for its Development Costs incurred in the performance of the activities set forth on **Schedule 3.3.3** (except those activities that are specifically in support of Phase Ib Trials or Phase II Trials for Alzheimer's Disease, including non-clinical support specific to such Clinical Studies); *provided* that [***].

3.3.4 Transition Plan Costs. Except as provided in **Section 3.3.3** (Initial Transition Activities), each Party shall be responsible for its FTE Costs and any Out-of-Pocket Costs incurred by such Party in performing disclosure and transfer activities pursuant to this **Section 3.3** (Disclosure of Technology for Development Purposes) or otherwise pursuant to the Technology Transfer Plan, including all materials for both the CNS Program and the Peripheral Program. In addition, notwithstanding the above, neither Party shall be obligated to provide or make available to the other Party research tools, materials or Information generally applicable to Development of products for the treatment of diseases or conditions, to the extent such items are not reasonably necessary for the other Party to further Develop or Manufacture the applicable Compounds or Products in the Territory under this Agreement.

3.4 Regulatory Matters.

3.4.1 Peripheral Program. Sanofi shall be responsible for, and bear the costs of, all regulatory activities with respect to Peripheral Compounds and Peripheral Products, *provided*, *however*, that Denali shall provide Sanofi with reasonable assistance as set forth in the Technology Transfer Plan, and otherwise as mutually agreed by the Parties.

3.4.2 CNS Program Regulatory Lead. On jurisdiction-by-jurisdiction basis for a CNS Product: (a) Denali shall be the Regulatory Lead with respect to regulatory matters and interactions related to the Denali CNS Development Activities with respect to such CNS Product (or, if earlier, Denali's exercise of the Denali Royalty Option pursuant to **Section 7.8** (Denali Royalty Option) with respect to such CNS Product); and (b) Sanofi shall be the Regulatory Lead with respect to regulatory matters and interactions related to (i) the Sanofi CNS Development Activities, or (ii) all Commercialization activities for such CNS Product.

3.4.3 CNS Program Regulatory Activities. The following shall apply with respect to regulatory activities relating to the CNS Program:

(a) **CNS Program Regulatory Lead**. Subject to **Section 3.4.3(c)** (CNS Program Major Market Involvement), the applicable Regulatory Lead shall have the lead role and responsibility with respect to the preparation, obtaining and maintenance of all Regulatory Documentation necessary to perform the applicable activities under the CNS Development Plan or Commercialization Plan. The Non-Regulatory Lead shall support the Regulatory Lead, as may be reasonably necessary, in the preparation, obtaining and maintenance of such Regulatory Documentation, and in the activities in support thereof, including providing necessary documents or other materials required by Applicable Law to obtain such Regulatory Approvals, in each case in accordance with the terms and conditions of this Agreement.

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(b) **CNS Program Regulatory Documentation**. All Regulatory Documentation to the extent relating to a CNS Compound or CNS Product with respect to an Indication within the CNS Program shall be owned by, and shall be the sole property and held in the name of the then-Regulatory Lead for such Indication, subject to the then-Non-Regulatory Lead's right to use such Regulatory Documentation in accordance with the licenses granted under **Article 6** (License Grants; Exclusivity). All Regulatory Documentation relating to the CNS Compounds or CNS Products that is not specific to any particular Indication shall be owned by, and shall be the sole property and held in the name of Sanofi, subject to Denali's right to use such Regulatory Documentation in accordance with the licenses granted under **Article 6** (License Grants; Exclusivity). In the event one Party replaces the other Party as the Regulatory Lead, the Parties shall, in manner consistent with the Transition Plan: (i) transition to such Regulatory Lead all applicable INDs for the applicable CNS Product and Indication; (ii) hereby assign to such Regulatory Lead all of such other Party's right, title and interest in and to all Regulatory Documentation (to the extent consistent with the above provisions of this **Section 3.4.3(b)** regarding ownership of such Regulatory Documentation) in the Territory and Controlled by such other Party during the Term; and (iii) duly execute and deliver, or cause to be duly executed and delivered, such instruments and shall do and cause to be done such acts and things, including the filing of such assignments, agreements, documents, and instruments, as may be necessary under, or as such Regulatory Lead may reasonably request to carry out more effectively the purpose of this **Section 3.4.3(b)**.

(c) **CNS Program Major Market Involvement**. The Regulatory Lead in a Major Market for the applicable CNS Compounds and CNS Products and the applicable Indication shall provide the Non-Regulatory Lead with an opportunity to review and comment on the Regulatory Lead's regulatory strategy for obtaining Regulatory Approvals for such CNS Products, and all Major Market Regulatory Filings for such CNS Compounds and CNS Products (collectively, "**Major Market CNS Regulatory Filings**"). The Regulatory Lead shall consider in good faith the Non-Regulatory Lead's comments and use reasonable efforts to implement such comments. The Regulatory Lead shall provide access to interim drafts of such Major Market CNS Regulatory Filings to the Non-Regulatory Lead via the access methods (such as secure databases) established by the JDC, and the Non-Regulatory Lead shall provide its comments on the final drafts of such Major Market CNS Regulatory Filings or of proposed material actions within [***] (or [***] in the case of Drug Approval Applications), or such other period of time mutually agreed to by the Parties. In the event that a Regulatory Authority in the Territory establishes a response deadline for any such Major Market CNS Regulatory Filing (or material action with respect thereto) shorter than such [***] period (or [***] period in the case of Drug Approval Applications), the Parties shall work cooperatively to ensure the Non-Regulatory Lead has a reasonable opportunity for review and comment within such deadlines.

(d) **CNS Program Regulatory Authority Visits**. The Regulatory Lead shall provide the Non-Regulatory Lead with prior written notice, to the extent the Regulatory Lead has advance knowledge, of any scheduled substantive meeting, conference, or discussion (including any advisory committee meeting) with a Regulatory Authority in the Major Markets relating to the CNS Program, within [***] after the Regulatory Lead first receives notice of the scheduling of such substantive meeting, conference, or discussion, unless the Regulatory Lead believes it is reasonably necessary for such substantive meeting, conference or discussion to occur

within [***] of scheduling, in which case such notice to the Non-Regulatory Lead shall be made as soon as practicable to provide the Non-Regulatory Lead a reasonable opportunity to attend such meeting, conference, or discussion. The Non-Regulatory Lead shall have the right to have up to [***] of its employees participate in all such substantive meetings, conferences, and discussions. The Regulatory Lead will provide the other Party with a copy of any correspondence from or to the Regulatory Authority, including any reports, such as meeting minutes, or findings issued by the Regulatory Authority in connection with an audit by such Regulatory Authority or otherwise.

(e) **CNS Program Cost Profit Sharing**. All costs incurred with respect to regulatory activities relating to: (i) the CNS Development Plan shall be a Shared Development Cost borne or shared by the Parties in accordance with **Section 7.7** (Cost Profit Sharing); (ii) the Co-Commercialization Plan pertaining to Commercialization activities for CNS Products in each country of the Cost Profit Sharing Countries, shall be an Allowable Expense; or (iii) any other Development or Commercialization activities shall be borne by the Party who incurred such costs; *provided* that, from and after the Co-Funding End Date following Denali's exercise of the Denali Royalty Option with respect to a particular CNS Product or all Products included in the CNS Program, each Party shall be solely responsible for all such costs incurred by such Party with respect to such CNS Product or the CNS Program, as the case may be.

3.4.4 Regulatory Data. To the extent not provided pursuant to **Section 3.3** (Disclosure of Technology for Development Purposes), the JDC shall establish a process pursuant to which each Party shall promptly provide to the other Party copies of or access to non-clinical data and Clinical Data, and other Information, results, and analyses with respect to any Development activities for the CNS Program and its Additional CNS Development Activities (collectively, "**Regulatory Data**").

3.5 Records. Each Party shall maintain records in accordance with its standard practices, which shall be consistent with standard practices in the pharmaceutical industry and in compliance with Applicable Law. Such records shall be retained by such Party for at least [***] after the Calendar Year to which such records relate, or for such longer period as may be required by Applicable Law. Upon request, such Party shall provide copies of the records it has maintained pursuant to this **Section 3.5** to the other Party.

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3.6 Clinical Trial Register and Data Transparency. The JDC will establish timelines and procedures for reviewing any public disclosure of Clinical Data, which procedures will include review and approval by [***] before any public disclosure. For the CNS Program, the applicable Development Lead will, and for the Peripheral Program, Sanofi will, in accordance with Applicable Law and its internal data transparency policies, publish the results or summaries of Clinical Studies relating to a Compound or Product on a clinical trial register maintained by it and the protocols of clinical trials relating to such Compound or Product on www.ClinicalTrials.gov (or an equivalent register, or as otherwise required by Applicable Law or such Party's policies). In the event that the data transparency policies of the other Party (regardless if such policy is based upon Applicable Law or other internal guidelines) are materially different to the data transparency policies of the applicable Development Lead (with respect to the CNS Program) or Sanofi (with respect to the Peripheral Program), as the case may be, the JDC shall meet in good faith to resolve such material differences, *provided* that neither

Party shall be permitted to prevent the disclosure of data by the other Party as required by such other Party's data transparency policies.

3.7 Patient Samples. With respect to the CNS Program, the Development Lead for the applicable Clinical Trial shall retain and archive all clinical samples obtained by such Party in the course of such Clinical Trial ("**CNS Patient Samples**"), and shall provide the other Party reasonable access to such retained CNS Patient Samples, including for use by a Party for activities outside the scope of this Agreement to the extent there are CNS Patient Samples available for use and there would be sufficient CNS Patient Samples remaining for use in connection with the CNS Program under this Agreement. All patient samples collected and retained in connection with Clinical Studies involving a Peripheral Compound or Peripheral Product (together with compilations of Information comprising annotations regarding patient histories or correlating patient outcomes, with respect to such samples, "**Peripheral Patient Samples**") shall, as between the Parties, be owned by Sanofi. Each Party shall use CNS Patient Samples and Peripheral Patient Samples in accordance with Applicable Law, including any informed consent and institutional review board regulations and all applicable requirements relating to the protection of human subjects.

3.8 Regulatory Audits by a Party. The Regulatory Lead for a CNS Product and Sanofi with respect to Peripheral Products may conduct audits of the other Party's, including of its and, to the extent permitted, its Third Party Providers', Regulatory Documentation (including reports from an audit conducted by a Regulatory Authority and any material correspondence relating thereto) or other records, Manufacturing and premises from time to time upon reasonable advance notice and during regular business hours as reasonably deemed necessary or appropriate by the inspecting Party to ensure compliance with GCP, GLP, GMP, Regulatory Approvals or other requirements of Regulatory Authorities applicable to the Compounds or Products. Denali shall promptly notify Sanofi of any audit conducted by a Regulatory Authority of Denali, or Affiliates of Denali, or Third Party Providers of Denali or its Affiliates to the extent known to Denali, and, in each case, to the extent relating to a Compound or Product.

ARTICLE 4
MANUFACTURING

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

4.1 Manufacturing Transfer. As soon as practicable after the Effective Date, Denali shall (i) transfer to Sanofi, at no cost to Sanofi, all inventories of raw materials, starting materials, Licensed Compounds, reference standards (Licensed Compounds and impurities) and Licensed Products; and (ii) transfer to Sanofi the Manufacturing of Licensed Compounds and Licensed Product as further described in the Technology Transfer Plan ("**Manufacturing Transfer**"), in each case (i) and (ii) except for those quantities as are necessary for Denali to perform the activities allocated to Denali under the Technology Transfer Plan or the CNS Development Plan, and to perform its Manufacturing obligations under **Section 4.2** (Manufacturing Responsibility). Notwithstanding anything to the contrary in this Agreement, the Manufacturing Transfer shall be subject to the terms and conditions of the agreements between Denali and its applicable Third Party Providers of manufacturing services and technology with respect to Licensed Compounds and Licensed Products (each agreement, a "**CMO Supply Agreement**") listed on **Schedule 4.1**. Each Party will be responsible for its own FTE Costs incurred in performing the Manufacturing Transfer with respect to the Licensed Compounds and Licensed Products, and Sanofi shall be responsible for all Out-of-Pocket Costs incurred in performing such Manufacturing Transfer, and shall reimburse Denali for any such Out-of-Pocket Costs incurred by Denali in performing such Manufacturing Transfer. Promptly after the Effective Date, Denali shall provide access to Sanofi to all necessary documentation (including copies of quality agreements in place between Denali and its Third Party Providers for the Manufacture of such Licensed Compounds or Licensed Products) and access to relevant Third Party Providers to allow Sanofi to coordinate its anticipated activities with such Third Party Providers, including the release by Sanofi, for use in Clinical Studies, of inventories of Licensed Compounds or Licensed Products transferred by Denali to Sanofi pursuant to (i) hereof.

4.2 Manufacturing Responsibility. Until completion of the Manufacturing Transfer, Denali shall be responsible for Manufacturing or having Manufactured each Licensed Compound and Licensed Product. Following completion of the Manufacturing Transfer, Sanofi shall be solely responsible for Manufacturing Compounds and Products, except that (a) Denali shall retain responsibility for Manufacturing, and supplying Sanofi with, quantities of Licensed Compounds and Licensed Products as further described on **Schedule 3.3.3**, and (b) Denali shall retain the right to Manufacture (or have Manufactured by a Third Party) quantities of Compounds and Products (i) for use in Additional Development Activities conducted by Denali, and (ii) to conduct formulation development activities in support of such Additional Development Activities.

4.3 Manufacturing Costs. All Manufacturing Costs incurred (a) in furtherance of the CNS Development Plan shall be a Development Cost borne by a Party or a Shared Development Cost shared by the Parties in accordance with **Section 7.7** (Cost Profit Sharing); (b) in furtherance of the Co-Commercialization Plan pertaining to Commercialization activities for CNS Products in each country of the Cost Profit Sharing Countries, shall be an Allowable Expense; or (c) in furtherance of (i) any Additional CNS Development Activities, or (ii) other Commercialization activities for the CNS Program not covered in the foregoing clause (b), shall be borne by the Party who incurred such costs; *provided* that, if Denali exercises the Denali Royalty Option, Sanofi shall, from and after the Co-Funding End Date with respect to the particular Cost Profit Sharing Opt Out Product for sales in the applicable Cost Profit Sharing Opt Out Country, bear all Manufacturing Costs with respect to the applicable Cost Profit Sharing Opt Out Product for sales in the applicable Cost Profit Sharing Opt Out Country (including, for the avoidance of doubt, any CNS Compound(s)

contained therein) and, to the extent that Denali Manufactures any such Cost Profit Sharing Opt Out Product or CNS Compound therein for sales in the applicable Cost Profit Sharing Opt Out Country, shall reimburse Denali for its Manufacturing Costs incurred in connection with the Manufacture of such Cost Profit Sharing Opt Out Product or CNS Compound therein for sale in the applicable Cost Profit Sharing Opt Out Country. Sanofi shall bear all Manufacturing Costs for Peripheral Compounds and Peripheral Products and, to the extent that Denali Manufactures any Peripheral Compounds or Peripheral Products, Sanofi shall reimburse Denali for its Manufacturing Costs incurred in connection with the Manufacture of Peripheral Compounds and Peripheral Products.

4.4 Supply Agreements. If, in a given country or region, a Party ("**Non-Manufacturing Party**") requires Compound or Product for the conduct of activities under a Program and the other Party ("**Manufacturing Party**") is responsible for Manufacturing such Compound or Product, then, upon either Party's request, the Parties shall enter into separate supply and associated quality agreements (each, a "**Supply and Quality Agreement**") covering the terms of supply to such Party for such activities. The Supply and Quality Agreement will contain terms and conditions that are reasonable and customary for agreements of such nature, including a right of the Non-Manufacturing Party to include its Manufacturing Costs as Shared Development Costs or Allowable Expenses, as applicable and to the extent provided in **Section 7.7** (Cost Profit Sharing), or if such Manufacturing Costs are not Shared Development Costs or Allowable Expenses in accordance with **Section 7.7** (Cost Profit Sharing), the Non-Manufacturing Party shall reimburse the Manufacturing Party for such Manufacturing Costs. If the Parties are unable to reach agreement on such provisions within [***] of a request by either Party to enter into a Supply and Quality Agreement (which [***] period may be extended upon the mutual agreement of the Parties), upon request by either Party, the same shall be determined pursuant to **Section 15.6.3** (ADR). The terms of any such Supply and Quality Agreement, including the Manufacturing Party's and the Non-Manufacturing Party's respective rights and obligations under such Supply and Quality Agreement, shall be consistent with, and limited by, rights and obligations of the Manufacturing Party under any applicable CMO Supply Agreements. To the extent there is any conflict between the terms and conditions of such Supply and Quality Agreements and this Agreement with respect to the matters expressly covered by such Supply and Quality Agreements, then such Supply and Quality Agreements shall control.

4.5 Manufacture Working Group. The JSC shall establish a manufacture working group ("**Manufacture Working Group**") to coordinate the Manufacturing Transfer activities by the Parties as set forth in **Section 4.1** (Manufacturing Transfer) and to assist the JSC in its responsibility with respect to the review and resolution of Manufacturing matters.

ARTICLE 5
COMMERCIALIZATION

5.1 General. Subject to the terms of this Agreement, including **Section 2.3** (Joint Commercialization Committee) and **Section 2.5** (Discontinuation of Joint Committees), the JCC or the JSC, as applicable, shall oversee and, to the extent applicable, coordinate, the Commercialization of Compounds and Products in the Territory.

5.2 Commercialization Activities.

5.2.1 Efforts. With respect to [***], Sanofi shall use Commercially Reasonable Efforts to commercialize such [***] for at least [***] years after [***] is obtained. Each Party shall [***]. Each Party shall perform any and all of its Commercialization activities with respect to each Program in compliance with all Applicable Law.

5.2.2 Allocation of Peripheral Program Activities and Costs. Sanofi shall be responsible for, and bear the cost of, all Commercialization activities with respect to the Peripheral Program.

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5.2.3 Allocation of Program Activities and Costs. Sanofi shall be responsible for, and bear the costs of, all Commercialization activities with respect to the Programs, subject to (a) Denali's rights to (i) engage in Co-Commercialization Activities under **Section 5.2.4** (Co-Commercialization Option in U.S. and China), and activities related to such Co-Commercialization Activities pursuant to the other provisions in this Article 5 (Commercialization), and (ii) participate in Cost Profit Sharing under **Section 7.7** (Cost Profit Sharing); and (b) Denali's obligations with respect (i) any such Co-Commercialization Activities under this Article 5 with respect to which Denali has exercised the Co-Commercialization Option, or (ii) Cost Profit Sharing under **Section 7.7** (Cost Profit Sharing) for each Cost Profit Sharing Product until the Co-Funding End Date for such Cost Profit Sharing Product, if applicable.

5.2.4 Co-Commercialization Option in U.S. and China.

(a) **Co-Commercialization Option**. For each of the United States and China, subject to **Section 5.2.4(b)** (Co-Commercialization Agreement), Denali shall have an option ("**Co-Commercialization Option**") to elect to provide between [***] and [***] of the Detailing efforts and MSL Activities for each CNS Product in the relevant country for Indications [***] (such percentage range, the "**Denali Activities Range**"), such activities, collectively, the "**Co-Commercialization Activities**" and either such country, once elected, is part of the "**Co-Commercialization Territory**" and is a "**Co-Commercialization Country**" and for so long as the Parties are engaged in Co-Commercialization Activities with respect to such CNS Product in such Co-Commercialization Country, such CNS Product is a "**Co-Commercialization Product**"). For purposes of the preceding sentence, any efforts with respect to electronic contacts by means of information technology (*e.g.*, videoconferencing) by or on behalf of either Party shall not be considered in determining the percentage of Detailing efforts and MSL Activities provided by Denali. Denali may exercise the Co-Commercialization Option for each such CNS Product in each such country (on a country-by-country and CNS Product-by-CNS Product basis) by (a) providing written notice to Sanofi no later than [***] before the anticipated Commercial launch of the applicable CNS Product in such country; and (b) reasonably demonstrating to Sanofi that Denali has, or will have on a timely basis, resources in place sufficient to perform Denali's share of the Co-Commercialization Activities for such CNS Product in such country.

(b) **Co-Commercialization Agreement**. The first time Denali exercises the Co-Commercialization Option for a CNS Product in a Co-Commercialization Country, the Parties shall negotiate in good faith terms and conditions of a co-commercialization agreement pursuant to which they will conduct the Co-Commercialization Activities for such CNS Product in the applicable country ("**Co-Commercialization Agreement**") and, to the extent Denali exercises its Co-Commercialization Option for any other CNS Product in such Co-Commercialization Country, the applicable Co-Commercialization Agreement shall be updated to include such CNS Product. The Co-Commercialization Agreement will contain the terms and conditions set forth on **Schedule 5.2.4** and such other terms as are agreed upon by the Parties; *provided* that in the event of any conflict between the terms of a Co-Commercialization Agreement and the terms of this Agreement (including **Schedule 5.2.4**), the terms of this Agreement shall control. The Parties shall use Commercially Reasonable Efforts to enter into the Co-Commercialization Agreement no later than [***] following the date upon which Denali exercises the Co-Commercialization Option, or

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such later date as the Parties may agree in writing. Until the Parties enter into the Co-Commercialization Agreement, the terms of this Agreement, including those set forth in **Schedule 5.2.4**, shall govern the Parties' Co-Commercialization Activities (during such period, references in **Schedule 5.2.4** to the Co-Commercialization Agreement shall be deemed to be references to **Schedule 5.2.4**) and, for the avoidance of doubt, Denali shall have the right to conduct Co-Commercialization Activities in accordance with the terms of this Agreement.

(c) **Termination of Co-Commercialization Activities Following Exercise of Denali Royalty Option**. If Denali exercises the Denali Royalty Option for a Cost Profit Sharing Product in a Cost Profit Sharing Country, then Denali's right and responsibility to conduct its portion of the Co-Commercialization Activities in such country for the applicable Cost Profit Sharing Opt Out Product will terminate over a reasonable transition time as specified in this **Section 5.2.4(c)**; *provided*, *however*, that (i) unless Sanofi notifies Denali otherwise, Denali's Co-Commercialization Activities would not terminate if Denali exercises the Denali Royalty Option with respect to a particular Cost Profit Sharing Product in a Cost Profit Sharing Country at a time between [***] before the anticipated date of the launch (as determined by JCC and for which Denali has received written notice) of the relevant Cost Profit Sharing Product in such Cost Profit Sharing Country and [***] following such launch (such time period, the "**Launch Window**"); and (ii) with respect to any time period outside of the Launch Window, [***] shall be a presumptively reasonable transition period, subject to the Parties' reasonable determination and agreement otherwise. Notwithstanding the foregoing, in no event shall Denali be responsible for any Allowable Expenses with respect to a Cost Profit Sharing Opt Out Product in a Cost Profit Sharing Opt Out Country after the Co-Funding End Date for such Cost Profit Sharing Opt Out Product pursuant to **Section 7.8.1** (Exercise by Denali) and, to the extent that the JCC requests Denali to continue to conduct any Co-Commercialization Activities after the Co-Funding End Date and during the Launch Window for a particular Product in a particular Cost Profit Sharing Country, Sanofi shall reimburse the FTE Costs and Out-of-Pocket Costs incurred by Denali in the conduct of such Co-Commercialization Activities that would have been Allowable Expenses had the Co-Funding End Date not occurred.

(d) **Termination of Co-Commercialization**. At any time after exercising the Co-Commercialization Option for a country, Denali may notify the JCC of Denali's desire to terminate all of its involvement in the Co-Commercialization Activities for any one or more of the CNS Products in such Co-Commercialization Country. The Parties, through the JCC, will endeavor to make arrangements that transition such activities to Sanofi over a reasonable time determined by the JCC but not to exceed [***] from the date of such notice from Denali unless such notice is delivered during the Launch Window, in which case such [***] period shall begin as of the date of the end of such Launch Window. If Denali exercises the Denali Royalty Option and continues to incur any FTE Costs or Out-of-Pocket Costs pursuant to such a transition of Co-Commercialization Activities following the applicable Co-Funding End Date for the subject Cost Profit Sharing Product, then Sanofi shall reimburse Denali such FTE Costs and Out-of-Pocket Costs. If Denali's transition after terminating Co-Commercialization Activities for a Cost Profit Sharing Product all occurs during a time while the product remains a Cost Profit Sharing Product, then Denali's FTE Costs or Out-of-Pocket Expenses shall continue to be allocated towards Allowable Expenses until such transition is complete.

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5.2.5 Commercialization Reports. For each Program, each Party shall report on the Commercialization activities such Party has performed (or caused to be performed) under such Program in accordance with the procedures established by (a) in the case of the CNS Program, the JCC and in any case no less frequently than once every [***]; and (b) in the case of the Peripheral Program, the JSC and in any case no less frequently then once every [***]. The JCC (in the case of the CNS Program) or the JSC (in the case of the Peripheral Program) shall evaluate the work performed in relation to the goals of the applicable Commercialization Plan. Each Party shall provide such other Information pertaining to its Commercialization activities for Products as reasonably requested by the JCC (in the case of the CNS Program) or the JSC (in the case of the Peripheral Program). Sanofi shall also consider in good faith Denali's views on pricing of the CNS Products in the Co-Commercialization Territory through the JCC.

5.3 Commercialization Plans.

5.3.1 Global Commercialization Plan. Reasonably in advance of the first Regulatory Approval for the first Product within each Program, Sanofi shall prepare for the JSC's review and comment a Global Commercialization Plan for Products within such Program. Such plan shall include: (a) an outline for the strategy for the Commercial launch of, and subsequent Commercialization of, each such Product in at least the Major Markets; (b) a summary of pre-launch Commercialization activities to be taken, including procurement of any necessary pricing and governmental reimbursement approvals for each such Product in at least the Major Markets; (c) general marketing and promotional plans for each such Product worldwide; and (d) an estimated annual sales forecast for such Products worldwide. The JSC shall agree upon the appropriate level of detail to be included in the respective Global Commercialization Plan, but the Global Commercialization Plan does not need to duplicate the content of any Co-Commercialization Plan.

5.3.2 Co-Commercialization Plan. For any CNS Product that is the subject of Cost Profit Sharing in a Cost Profit Sharing Country, Sanofi shall prepare, in consultation with Denali and for discussion, review and approval by the JCC (or if such CNS Products are not also Co-Commercialization Products, by the JSC), a detailed Co-Commercialization Plan for the Commercialization of such CNS Products in such country. The Co-Commercialization Plan for a Cost Profit Sharing Country shall include:

(a) [***];

(b) [***];

(c) a non-binding sales and marketing forecast for such country;

(d) a non-binding projection of Net Sales of such CNS Products for such country;

(e) [***];

(f) [***];

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(g) for those CNS Products in a country where the Co-Commercialization Option has been exercised pursuant to **Section 5.2.4** (Co-Commercialization Option in U.S. and China) by Denali for one or more CNS Products, the allocation of Co-Commercialization Activities between the Parties to be undertaken with respect to each of the CNS Products in the applicable country, including the allocation of responsibility for the conduct of any MSL Activities and Detailing, including the geographic allocation of each Party's sales representatives (consistent with this **Section 5.3.2**); and

(h) a Co-Commercialization Budget with respect to the Commercialization Activities for each Cost Profit Sharing Product in such country.

For each Co-Commercialization Country, the Co-Commercialization Plan shall allocate Co-Commercialization Activities between the Parties, taking into consideration the Parties' respective actual or reasonably anticipated capabilities, infrastructure and resources in the applicable country, as the case may be, relevant to the CNS Program at the time of expected First Commercial Sale of the CNS Products therein. Notwithstanding the foregoing, if Denali exercises the Co-Commercialization Option the Co-Commercialization Plan shall provide for sales representatives of each Party to be deployed in at least some of the major metropolitan areas in such country.

5.3.3 Amendments and Updates. The JCC (or if applicable, the JSC) shall review the Commercialization Plans (including, if applicable, the associated Co-Commercialization Budget) on a regular basis, and in no event less frequently than once every [***] (as provided below), or more frequently as needed to take into account completion, commencement or cessation of Commercialization activities contemplated in the then-current applicable Commercialization Plan for, as well as any newly available Information related to, such Program. Either Party, through its representatives on the JCC (or if applicable, the JSC), may propose amendments to, or comments on, a Commercialization Plan (or, if applicable, the associated Co-Commercialization Budget) for a given Program from time to time. Amendments to the Co-Commercialization Plan shall be subject to approval in accordance with **Section 2.4.5** (Joint Committee Decision Making). In any event, an updated Commercialization Plan, including the associated Co-Commercialization Budget (if applicable), shall be provided by the JCC (and approved by the JSC as required) (or if applicable, provided to and approved by the JSC) no later than November 20 of each Calendar Year. If a revised Co-Commercialization Plan

(and associated Co-Commercialization Budget) is not approved by the JSC by December 15 of a Calendar Year, then, until such time as such a revised Co-Commercialization Plan (and associated Co-Commercialization Budget (if applicable)) is approved in accordance with **Section 2.4.5** (Joint Committee Decision Making): (a) the then-current Co-Commercialization Plan (and associated Co-Commercialization Budget) shall continue to govern the Parties' Commercialization activities under this Agreement with respect to the CNS Program in the Co-Commercialization Territory; and (b) each Party shall be permitted to conduct the activities allocated to such Party in such then-current Co-Commercialization Plan and to incur costs consistent with such associated Co-Commercialization Budget, which costs (with respect to the Cost Profit Sharing Products in each Cost Profit Sharing Country) shall be shared by the Parties as Allowable Expenses in accordance with **Section 7.7** (Cost Profit Sharing).

5.4 CNS Program Activities involving Sales Representatives.

5.4.1 Conduct of Sales Representatives. If Denali exercises its Co-Commercialization Option pursuant to **Section 5.2.4** (Co-Commercialization Option in U.S. and China) with respect to any Co-Commercialization Country, then with respect to each such country, the following shall apply:

(a) **Statements by Sales Representatives**. Denali and Sanofi shall each ensure that its sales representatives do not make any representation, statement, warranty or guaranty with respect to a CNS Product that is not consistent with the applicable, current package insert of prescribing information or other documentation accompanying or describing such CNS Product, including mutually approved limited warranty and disclaimers, if any. Denali and Sanofi shall each ensure that its sales representatives do not make any statements, claims or undertakings to any person with whom they discuss or promote CNS Products that are not consistent with, nor provide or use any labeling, literature or other materials other than, those Promotional Materials currently approved for use by the JCC in the applicable country of the Co-Commercialization Territory. If at any time Sanofi no longer approves the use of specified Promotional Materials in any country of the Co-Commercialization Territory, each Party shall take appropriate action to remove the Promotional Materials from use, destroy such Promotional Materials or otherwise modify such Promotional Materials for an approved use.

(b) **Training Materials Review**. Denali shall have the right to review and comment on the training materials and programs to be used in such markets prior to the implementation of such training materials and programs, in accordance with reasonable processes established by the JCC, and Sanofi shall give good faith consideration to Denali's comments regarding such training materials and programs, including any comments related to the training materials' and programs' compliance with Applicable Law.

(c) **Compliance with Laws**. Denali and Sanofi shall each cause its sales representatives performing activities under the Co-Commercialization Plan to comply with Applicable Law and industry guidelines related to the performance of its obligations hereunder.

(d) **Activity Recordkeeping**. Each Party shall maintain records of its sales representatives' activities relating to CNS Products in each applicable country of the Co-

Commercialization Territory and each Party shall allow representatives of the other Party to inspect such records upon request during normal business hours and upon reasonable prior notice.

(e) **KPI Dashboards**. Sanofi shall, with Denali's assistance as reasonably requested by Sanofi and solely to the extent Denali possesses relevant information, establish a performance dashboard that visually tracks, analyzes and displays key performance indicators (KPI), metrics and key data points relating to market shares, net sales and sales activities to be presented at each JCC meeting. Each Party shall cause its sales representatives to record and report their Detailing activities using an auditable customer relationship management ("**CRM**") tool.

5.4.2 Calculation of Sales Force Costs. For the purposes of calculating the FTE Costs of each Party's sales representatives performing activities in each Cost Profit Sharing Country under the applicable Co-Commercialization Plan, the FTE Rate shall be deemed to be [***] of the applicable FTE Rate pursuant to **Section 1.61** ("FTE Rate" definition) for such sales representative on a full-time basis; *provided* that for each sales representative who also engages in promotion activities for a product other than a CNS Product during the relevant Calendar Quarter, the cost of such sales representative (for purposes of calculating Allowable Expenses) shall be reduced proportionately based on the Detail position of such other product(s) during such sales activities and a reasonable apportionment of the value of such Detail position(s) for such other product(s). For such purposes: (i) in a two-product Detail, the first position Detail shall be deemed [***] and the second position shall be deemed [***] of the value of the product Detail; (ii) in a three-product Detail, the first position Detail shall be deemed [***], the second position shall be deemed [***] and the third position shall be deemed [***] of the value of the product Detail; and (iii) the value of other similar multi-product promotions shall be allocated in a similar way. For example, if a sales representative who is promoting only a Cost Profit Sharing Product in a Cost Profit Sharing Country and no other products in a Calendar Quarter, [***] of the FTE Rate for such sales representative shall be included for purposes of calculating the Allowable Expenses for such Calendar Quarter, whereas if such sales representative is promoting one other product and such other product is in the second Detail position, only [***] of the FTE Rate for such sales representative shall be included in calculating the Allowable Expenses for such Calendar Quarter. For the purposes of calculating the FTE Costs of each Party's sales representatives performing activities in the Cost Profit Sharing Countries under the applicable Co-Commercialization Plan, the FTEs of contractor sales force shall be reported in the same FTE category as employee sales force and the FTE Rate for such contractor sales force FTEs shall be calculated in accordance with **Section 1.61** ("FTE Rate" definition); *provided* that the contractor sales force and medical science liaisons of a Party in a Cost Profit Sharing Country shall not exceed [***] of the sales force and medical science liaisons of such Party for such Cost Profit Sharing Product in such Cost Profit Sharing Country, unless mutually agreed otherwise by Parties; *provided*, *further*, that the foregoing restriction shall not apply to Denali until the expiration of the first [***] after the First Commercial Sale of the first Co-Commercialization Product in the applicable Co-Commercialization Country so long as employees of Denali acting as senior personnel equivalent to national or regional sales directors and national or regional directors of MSL Activities are responsible for managing such sales force and such medical science liaisons.

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5.5 Advertising and Promotional Materials. Sanofi shall develop relevant sales, promotion, market access and advertising materials (collectively, "**Promotional Materials**") in each case consistent with Applicable Law, the applicable Commercialization Plans and any determinations made by the JCC with respect to such matters pursuant to **Section 2.3.2** (Specific Responsibilities) (as applicable). Sanofi shall be responsible for the medical, regulatory and legal review of Promotional Materials and for the interpretation and adherence to the Applicable Law governing the preparation and use of such Promotional Materials, including any advance review of the Promotional Materials required by the applicable Regulatory Authority. Notwithstanding the foregoing, in the event Denali exercises its Co-Commercialization Option pursuant to **Section 5.2.4** (Co-Commercialization Option in U.S. and China) in any country within the Co-Commercialization Territory, Denali shall have the right to review and comment on the Promotional Materials for the applicable Co-Commercialization Product(s) to be used in each applicable Co-Commercialization Country prior to the implementation of such Promotional Materials, in accordance with the reasonable processes established by the JCC, and Sanofi shall give good faith consideration to Denali's comments regarding the Promotional Materials, including any comments related to the Promotional Materials' compliance with Applicable Law. Sanofi will own all right, title and interest in and to any and all Promotional Materials (except with respect to any Corporate Names of Denali included in any Promotional Materials). Denali will execute all documents and take all actions as are reasonably requested by Sanofi to vest title to such Promotional Materials in Sanofi.

5.6 Medical Inquiries. Except as assigned to Denali as part of the Co-Commercialization Plan, Sanofi shall handle all medical questions or inquiries from members of the medical profession in any country regarding the Products. In the event Denali exercises its Co-Commercialization Option in a country within the Co-Commercialization Territory, Denali shall, and shall cause its sales representatives or medical science liaisons (as applicable depending on the nature of the question or inquiry) to, refer to Sanofi all such questions and inquiries within [***] hours of receipt, unless earlier notification is required pursuant to the Pharmacovigilance Agreement or Applicable Law. Sanofi shall respond appropriately to all such inquires in a timely manner.

5.7 Product Packaging; Branding. Sanofi shall develop and approve packaging and Product Labeling for each Product, which in all cases shall be consistent with the Commercialization Plans and in accordance with Applicable Law. Sanofi shall also be responsible for determining medical communications, positioning, messaging, and branding for each Product in each jurisdiction or region; *provided* that positioning, messaging, and branding for each Product shall be consistent with the applicable Commercialization Plans and Applicable Law. Notwithstanding the foregoing, in the event Denali exercises its Co-Commercialization Option with respect to any country within the Co-Commercialization Territory, Denali shall have the right to review and comment on Product Labeling, as well as positioning, messaging, and branding, for each Co-Commercialization Product in such country(ies) of the Co-Commercialization Territory, all in accordance with the reasonable processes established by the JCC, and Sanofi shall give good faith consideration to Denali's comments regarding such matters.

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5.8 Sales and Distribution. Sanofi shall (a) book all sales of Products and (b) be responsible for warehousing and distributing the Products. If Denali receives any orders for a Product, it shall refer such orders to Sanofi in the applicable country or region.

5.9 Shipping and Returns. Sanofi shall be responsible for handling all returns of the Products. If a Product sold is returned to Denali, Denali shall promptly ship such Product to a facility designated by Sanofi. Sanofi shall also be responsible for handling all aspects of such Product order processing, invoicing and collection, distribution, inventory, and receivables for each jurisdiction or region.

5.10 Recalls, Market Withdrawals or Corrective Actions. In the event that any Regulatory Authority issues or requests a recall or takes a similar action in connection with a Product, or in the event either Party determines that an event, incident or circumstance has occurred that may result in the need for a recall or market withdrawal, in each case, in any jurisdiction or region, the Party notified of such recall or similar action, or the Party that desires such recall or similar action, shall, within [***] hours, advise the other Party thereof orally or in writing. Sanofi shall decide whether to conduct a recall in such jurisdiction or region and the manner in which any such recall shall be conducted, *provided* that Sanofi shall make such decision in consultation with Denali if the recall pertains to the CNS Program, except in the case of a government mandated recall or if Denali has exercised the Denali Royalty Option, in which case Sanofi may act without such advance notice or consultation, but shall notify Denali as soon as possible. Each Party shall make available to the other Party, upon request, all of such Party's pertinent records that such other Party may reasonably request to assist such other Party in effecting any recall.

5.11 Product Trademarks. [***].

5.12 Markings. To the extent required by Applicable Law in a country or other jurisdiction in the Territory, the Promotional Materials, packaging, and Product Labeling for the Licensed Products shall contain the Corporate Name of both Sanofi and Denali.

5.13 Responsibility for Commercialization Costs. The costs and expenses of any activities conducted pursuant to **Section 5.4.2** (Calculation of Sales Force Costs), **Section 5.6** (Medical Inquiries), **Section 5.7** (Product Packaging; Branding), **Section 5.8** (Sales and Distribution), **Section 5.9** (Shipping and Returns) and **Section 5.10** (Recalls, Market Withdrawals or Corrective Actions) (a) for Cost Profit Sharing Products in each applicable Cost Profit Sharing Country shall be included in calculating Allowable Expenses, and (b) otherwise (including with respect to the Peripheral Program) such costs and expenses shall be the responsibility of Sanofi.

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ARTICLE 6
LICENSE GRANTS; EXCLUSIVITY

6.1 License Grants to Sanofi.

6.1.1 Grant. Subject to the terms and conditions of this Agreement (including **Section 6.1.2** (Certain Restrictions and Reservations)), Denali hereby grants to Sanofi:

(a) An exclusive (including exclusive of Denali) royalty-bearing license and Right of Reference, with the right to grant sublicenses and further Rights of Reference through multiple tiers in accordance with **Section 6.3.1** (By Sanofi), under the Denali Technology (including Denali's interest in the Joint Program Know-How and Joint Program Patents), to Exploit Licensed Compounds, Licensed Products, Sanofi Compounds and Sanofi Products, in the Field in the Territory; and

(a) A non-exclusive royalty-bearing license, with the right to grant sublicenses in accordance with **Section 6.3.1** (By Sanofi), to use Denali's Corporate Names solely as required by Applicable Law to Exploit Licensed Compounds, Licensed Products, Sanofi Compounds and Sanofi Products, in the Field in the Territory.

6.1.2 Certain Restrictions and Reservations. In no event shall Sanofi use (or authorize the use of) any Denali Technology (other than Joint Program Know-How and Joint Program Patents) except for the purposes of Exploiting Licensed Compounds, Licensed Products, Sanofi Compounds and Sanofi Products under and in accordance with this Agreement. Notwithstanding **Section 6.1.1** (Grant) and without limiting Denali's obligations under **Section 6.8** (Exclusivity) or any other applicable term of this Agreement, [***]. For the avoidance of doubt, Denali retains the right to use and otherwise Exploit (x) the Denali Technology for purposes of the Development, Manufacture or Commercialization of any compounds or products that are not Compounds or Products; and (y) Denali's Corporate Names for any and all purposes.

6.2 License Grants to Denali.

6.2.1 Grant. Subject to the terms and conditions of this Agreement (including **Section 6.2.2** (Certain Restrictions and Reservations)), Sanofi hereby grants to Denali:

(a) A license and Right of Reference, with the right to grant sublicenses and further Rights of Reference in accordance with **Section 6.3.2** (By Denali), under the Sanofi Technology (including Sanofi's interest in Joint Program Know-How and Joint Program Patents) and a sublicense under the rights in the Denali Technology granted to Sanofi under **Section 6.1** (License Grants to Sanofi) to Exploit CNS Licensed Compounds, CNS Licensed Products, Sanofi CNS Compounds and Sanofi CNS Products, in the Field in the Territory (i) in accordance with the applicable Development Plan (including pre-clinical and non-clinical activities for Indications within Alzheimer's Disease), (ii) for discovery and development of biomarkers in connection with the Program, (iii) the conduct of counter-screens in connection with medicinal chemistry efforts in connection with the Program, (iv) research purposes (including basic biology research to validate new Indications for RIPK1 Inhibitors) in connection with the Program, and (v) for the conduct of

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(A) Additional CNS Development Activities (including any pre-clinical, non-clinical and formulation development activities that may be appropriate to support such Additional CNS Development Activities and making (or having made) Compounds and Products for use in such Additional Development Activities), and (B) the applicable Co-Commercialization Plans, and such licenses granted to Denali under this **Section 6.2.1(a)** shall be exclusive with respect to the conduct of (x) Phase I Trial and Phase II Trial activities for Indications with Alzheimer's Disease that are set forth in the CNS Development Plan [***], and (y) any Clinical Study for a particular indication that is an Additional Development Activity conducted by Denali pursuant to **Section 3.2.4** (Additional CNS Program Development Activities), and otherwise the licenses granted to Denali under this **Section 6.2.1(a)** shall be non-exclusive;

(b) A non-exclusive license, with the right to grant sublicenses in accordance with **Section 6.3.2** (By Denali), to use Sanofi's Product Trademarks and Sanofi's Corporate Names solely as required by Applicable Law to Exploit Licensed CNS Compounds, Licensed CNS Products, Sanofi CNS Compounds and Sanofi CNS Products, in the Field in the Territory in accordance with **Section 5.12** (Markings), the applicable Development Plan and the applicable Co-Commercialization Plans; and

(c) A non-exclusive license and Right of Reference, with the right to grant sublicenses and further Rights of Reference in accordance with **Section 6.3.2** (By Denali), under the Denali Technology, Sanofi Technology (including Sanofi's interest in Joint Program Know-How and Joint Program Patents) and sublicense under the rights granted to Sanofi under **Section 6.1** (License Grants to Sanofi), to Exploit CNS Licensed Compounds, CNS Licensed Products, Sanofi CNS Compounds, Sanofi CNS Products, in the Field in the Territory for the conduct of the Technology Transfer Plan (including DMPK, biomarker and toxicology activities included therein).

6.2.2 Certain Restrictions and Reservations. In no event shall Denali use (or authorize the use of) any Sanofi Technology (other than Joint Program Know-How and Joint Program Patents) except for the purposes of Exploiting Licensed Compounds, Licensed Products, Sanofi CNS Compounds and Sanofi CNS Products, under and in accordance with this Agreement. Notwithstanding **Section 6.2.1** (Grant) and without limiting Sanofi's obligations under **Section 6.8** (Exclusivity), [***]. For avoidance of doubt, Sanofi retains the right to use and otherwise Exploit (x) the Sanofi Technology for purposes of the Development, Manufacture or Commercialization of any compounds or products that are not Compounds or Products; and (y) Sanofi's Corporate Names for any and all purposes.

6.3 Sublicenses; Licensing.

6.3.1 By Sanofi. Sanofi shall have the right to grant (i) sublicenses (or further Rights of Reference), through multiple tiers of sublicensees, under the licenses and Rights of Reference granted in **Section 6.1.1** (Grant), or (ii) licenses under the Sanofi Technology and Rights of Reference Controlled by Sanofi, in each case, to its Affiliates and other Persons; *provided* that any such sublicenses (and further Right of Reference) shall be [***].

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6.3.2 By Denali. Denali shall have the right to grant sublicenses (or further Rights of Reference) under the licenses and Rights of Reference granted to Denali under **Section 6.2.1** (Grant) to its Affiliates and other Persons; *provided* that any such sublicenses (and further right of reference) shall be [***]. Notwithstanding the foregoing, and without limiting its right to subcontract pursuant to **Section 6.4** (Subcontracting), Denali shall not have the right to, and shall not, grant any sublicense under the licenses and Rights of Reference granted in **Section 6.2.1** (Grant) to a Third Party Sublicensee: (a) [***]; and (b) [***].

6.3.3 Responsibility for Sublicensees. Each sublicensing Party (or Party whose Affiliate grants a sublicense) shall remain liable under this Agreement for the performance of all its obligations under this Agreement [***].

6.3.4 Have Rights. The grant of a right by a Party to "have made", "have used", "have sold", "have imported" or similar action to be taken solely on behalf, and for the sole benefit of, a Party or its Affiliate, whether implied or expressed in a contract with a Third Party Provider, without any other express license rights to be exercised by the grantee independently of the Party, *e.g.*, to independently "make", will be deemed to be a subcontract under **Section 6.4** (Subcontracting) if it otherwise meets the requirements of **Section 6.4** (Subcontracting) and not a sublicense that is the subject of **Section 6.3** (Sublicenses).

6.4 Subcontracting. Each Party and its Affiliates may subcontract the performance of any of its Development activities and Commercialization activities in the Territory with respect to a Program undertaken in accordance with this Agreement to one or more Third Party Providers pursuant to a Subcontract Agreement which shall be [***]; *provided* that:

(a) each Party shall keep the other Party reasonably informed with respect to any material activities such Party intends to subcontract and [***];

(b) the Subcontract Agreement shall (i) [***]; (ii) [***]; and (iii) [***];

(c) except with the written consent of the other Party (in its sole discretion), a Party shall not subcontract to a Third Party [***] more than [***] of those activities to be conducted by such Party in a particular [***]; *provided*, *further*, that the foregoing restriction shall not apply to Denali until the expiration of the first [***] after the [***] so long as employees of Denali [***]; and

(d) Denali may [***], *provided* that, for the avoidance of doubt, Denali shall [***].

Notwithstanding the foregoing, the subcontracting Party shall [***].

6.5 Third Party Intellectual Property.

6.5.1 Existing Denali In-License Agreements. It is understood that Denali's In-License Agreements existing as of the Execution Date and listed on **Schedule 6.5.1** (collectively, the "**Existing In-License Agreements**") may require that particular provisions be incorporated into

a sublicense granted thereunder. The requirements of any such provisions in the Existing In-License Agreements are set out on **Schedule 6.5.1** attached hereto and shall be deemed incorporated by reference into this Agreement for the sole purpose of the subject matter that is the subject of the sublicense. Each of Denali and Sanofi agrees to be bound by and comply with the provisions of each Existing In-License Agreement listed on **Schedule 6.5.1** to the extent applicable to Denali in its capacity as licensee of each such Existing In-License Agreement or Sanofi in its capacity as a sublicensee under each such Existing In-License Agreement for so long as the applicable Existing In-License Agreement is in full force and effect and thereafter [***].

6.5.2 New Technology.

(a) **For CNS Program**.

(i) **Acquisition Process**. [***]. If, after the Effective Date, a Party acquires, from any Third Party, [***] pertaining to a CNS Compound or CNS Product being Developed or Commercialized under this Agreement ("**New CNS Program Technology**"), the following shall apply:

(A) Promptly after such acquisition (or promptly after Additional CNS Development Opt-In Notice has been provided for any such Third Party rights acquired in connection with any Additional CNS Development Activities), such Party shall so notify the [***] and provide the [***] with a summary of the terms of any license or agreement under which such Party would acquire such New CNS Program Technology that would be applicable to such a CNS Compound or CNS Product (such applicable terms, "**New CNS Program Technology Terms**").

(B) In the event the [***] determines [***], then such New CNS Program Technology shall be included in Denali Technology or the Sanofi Technology, as the case may be, and subject to the terms and conditions of this Agreement and the Parties shall be bound by such New CNS Program Technology Terms.

(C) In the event the [***] does not make such determination, then such New CNS Program Technology shall thereafter be deemed excluded from the Denali Technology or Sanofi Technology, as the case may be, under this Agreement, [***].

(ii) **Cost Sharing**. If any New CNS Program Technology is subject to payment to a Third Party as a result of a Party's exercise of any such New CNS Program Technology in performance of activities under this Agreement, then (x) such amounts specifically allocable to the Regulatory Approval or sale of a Cost Profit Sharing Product in the applicable Cost Profit Sharing Country shall be included as Allowable Expenses, and (y) otherwise shall be borne by the Parties as mutually agreed, including with respect to Sanofi's rights to offset any such amounts against royalties otherwise due to Denali pursuant to **Section 7.5.4(c)** (In-License Agreements).

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(b) **For Peripheral Program**.

(i) **Acquisition Process**. If, after the Effective Date, a Party wishes to acquire from any Third Party [***] pertaining to a Peripheral Compound or Peripheral Product being Developed or Commercialized under this Agreement, or incorporate any Third Party [***] into any Peripheral Compound or Peripheral Product being Developed or Commercialized under this Agreement ([***], "**New Peripheral Program Technology**"), then, the following shall apply: (A) to the extent such New Peripheral Program Technology would be Denali Technology, Denali shall so notify Sanofi and provide Sanofi with a summary of the terms of any license or agreement under which Denali acquired such New Peripheral Program Technology (such applicable terms, "**Denali New Peripheral Program Technology Terms**"), and Sanofi shall have the right to elect whether to apply such New Peripheral Program Technology to Peripheral Compounds or Peripheral Products under this Agreement and included in the Denali Technology licensed to Sanofi hereunder; and (B) to the extent such New Peripheral Program Technology would be Sanofi Technology, Sanofi shall have the right to determine whether to apply such New Peripheral Program Technology to the Peripheral Compounds or Peripheral Products under this Agreement. In the event Sanofi elects in writing to include any such New Peripheral Program Technology in the Denali Technology, then such New Peripheral Program Technology shall be included in Denali Technology and subject to the terms and conditions of this Agreement and the Parties shall be bound by such Denali New Peripheral Program Technology Terms. In the event Sanofi does not elect in writing to apply such New Peripheral Program Technology to Peripheral Compounds or Peripheral Products, then such New Peripheral Program Technology shall thereafter be deemed excluded from the Denali Technology, as the case may be, under this Agreement.

(ii) **Cost Sharing**. If any New Peripheral Program Technology is subject to payment to a Third Party, as a result of the grant to Sanofi or rights with respect to any such New Peripheral Program Technology, or the exercise by Sanofi of any such New Peripheral Program Technology in performance of activities under this Agreement, then Sanofi shall pay (or, if applicable, reimburse Denali for) such amounts, subject to Sanofi's rights to offset applicable amounts pursuant to **Section 7.5.4(c)** (In-License Agreements).

6.5.3 Coordination with Third Party Agreements. The obligations of each Party and the rights of the other Party under this Agreement, [***], *provided* that [***]. If the [***] would (if followed) cause the Party to such an agreement [***], then [***]. If the Party to any such agreement [***], then, to the extent permitted by such agreement, such Party shall [***].

6.6 Retention of Rights.

6.6.1 By Denali. Except as expressly provided in this Agreement, Denali grants no other right or license to Sanofi under this Agreement, including any rights or licenses to the Denali Technology, the Regulatory Documentation, Denali's Corporate Names, or any other Patent or intellectual property rights not otherwise expressly granted herein, whether by implication, estoppel or otherwise.

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6.6.2 By Sanofi. Except as expressly provided in this Agreement, Sanofi grants no other right or license to Denali under this Agreement, including any rights or licenses to the Sanofi Technology, the Regulatory Documentation, Sanofi's Corporate Names, or any other Patent or intellectual property rights not otherwise expressly granted herein, whether by implication, estoppel or otherwise.

6.7 Confirmatory License Agreement. Each Party shall, if requested to do so by the other Party, promptly enter into confirmatory license agreements in the form, or substantially the form, reasonably requested by such other Party for purposes of recording the licenses granted under this Agreement with the applicable governmental offices as such other Party considers appropriate. Until the execution of any such confirmatory licenses, so far as may be legally possible, Denali and Sanofi shall have the same rights in respect of the Denali Technology and Sanofi Technology, as the case may be, and be under the same obligations to each other in all respects as if the said confirmatory licenses had been executed.

6.8 Exclusivity.

6.8.1 Joint Commitment. During the Term, each Party agrees for itself and its Affiliates to:

(a) [***], and

(b) [***],

in the case of each of (a) and (b), only [***].

6.8.2 Acquisitions of Competing Products. Notwithstanding the provisions of **Section 6.8.1** (Joint Commitment), if, during the Term:

(a) **Acquired Competing Product**. A Party or any of its Affiliates acquires rights to any [***] (any of the foregoing, a "**Competing Product**") through an Acquisition, such Acquisition, and the Development and Commercialization of such Competing Product thereafter, shall not constitute a breach of **Section 6.8.1** (Joint Commitment) if either (i) [***], or (ii) [***]. The acquiring Party shall notify the other Party in writing of its election (proviso (i) or (ii)) under this **Section 6.8.2(a)** within [***] from the closing of the Acquisition.

(a) **Change in Control Competing Product**. If a Party undergoes a Change in Control and the relevant acquirer or merger partner controls rights to any Competing Product(s), such Change in Control, and the subsequent Development, Manufacture and Commercialization of such Competing Product(s) by such relevant acquirer or merger partner, as the case may be, or any of its Affiliates, shall not constitute a breach of **Section 6.8.1** (Joint Commitment) if (i) [***], or (ii) [***] ("**Change in Control Effective Date**"); *provided*, *however*, that if (1) [***]; (2) [***]; and (3) [***] (ii) and [***], then the following will apply: (A) [***]; (x) notwithstanding **Section 2.3.2** (Specific Responsibilities), [***]; (y) Sanofi's obligations under **Section 6.8** (Exclusivity) [***]; and (z) notwithstanding **Section 5.2.4(a)** (Co-Commercialization Option), [***]. The acquired Party shall notify the other Party in writing of its election ((i) or (ii),

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including, with respect to (ii), [***] from the Change in Control Effective Date (the date of such notice, "**Competing Product Election Notice**").

ARTICLE 7
PAYMENTS

7.1 Upfront Consideration. Within [***] following the Effective Date, in partial consideration paid in return for those rights granted to Sanofi under this Agreement, Sanofi shall pay to Denali a one-time payment in the amount of One Hundred Twenty Five Million Dollars ($125,000,000) ("**Upfront Consideration**"). The Upfront Consideration shall not be refundable or creditable against any future payments by Sanofi to Denali under this Agreement.

7.2 CNS Program Milestones.

7.2.1 CNS Milestones. Sanofi shall pay to Denali, in accordance with **Section 7.4.2** (Reports and Payments for Milestones) and **Section 7.9** (Mode of Payment), the milestone payments set forth below (together with the amounts in **Section 7.2.2** [***], the "**CNS Milestone Payments**") following the [***] of each of the following corresponding development and regulatory milestone events (together with the development and regulatory milestone events in **Section 7.2.2** [***], each, a "**CNS Milestone**" as numbered in the following table) with respect to a CNS Product (subject to **Section 7.4** (Other Matters Regarding Milestones)):

CNS Milestone	CNS Milestone Payment
1. [***]	[***]
2. [***]	[***]
3. [***]	[***]
4. [***]	[***]
5. [***]	[***]
6. [***]	[***]
7. [***]	[***]
8. [***]	[***]
9. [***]	[***]
10. [***]	[***]
11. [***]	[***]
12. [***]	[***]
13. [***]	[***]
14. [***]	[***]

7.2.2 [***]. In addition to the amounts set out in **Section 7.2.1** (CNS Milestones), Sanofi shall pay to Denali, in accordance with **Section 7.4.2** (Reports and Payments for Milestones) and **Section 7.9** (Mode of Payment), additional CNS Milestone Payments if the Indication with respect to which a particular CNS Milestone is [***], as follows: (i) [***], and (ii) [***] under this **Section 7.2.2** shall be payable only once on the [***] of the applicable CNS Milestone by a CNS Product for [***], [***], and shall be payable in addition to any corresponding CNS Milestone

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Payment specified in the table in **Section 7.2.1** (CNS Milestones), if an [***] for which the applicable CNS Milestone is achieved. By way of example, [***].

7.2.3 Additional CNS Milestone Details. For purposes of **Section 7.2.1** (CNS Milestones):

(a) The CNS Product for the purposes of CNS Milestones [***] in the table in **Section 7.2.1** (CNS Milestones) may, but need not, be the same CNS Product;

(b) If, at the time of achievement of CNS Milestone [***] (or a requirement to pay the corresponding payment under this **Section 7.2.3**), a milestone payment corresponding to achievement of CNS Milestone [***] was not paid, then upon such achievement (or deemed achievement) of CNS Milestone [***], a milestone corresponding to such unpaid CNS Milestone [***] shall also become due and payable to Denali (unless the achievement of CNS Milestone [***] was by an Indication within [***]);

(c) If at the time of achievement of CNS Milestones [***] (or a requirement to pay the corresponding payment under this **Section 7.2.3**), a milestone payment corresponding to achievement of CNS Milestones [***] was not paid, then upon such achievement (or deemed achievement) of CNS Milestones [***], a milestone corresponding to such unpaid CNS Milestones [***] shall also become due and payable to Denali (except that Milestone [***] would not be payable if such achievement of CNS Milestone(s) [***] was by an Indication within [***]);

(d) If at the time of achievement of CNS Milestone [***] (or a requirement to pay the corresponding payment under this **Section 7.2.3**), a milestone payment corresponding to achievement of CNS Milestone [***] was not paid, then upon such achievement (or deemed achievement) of CNS Milestone [***], a milestone corresponding to such unpaid CNS Milestone [***] shall also become due and payable to Denali (except that CNS Milestone [***] would not be payable if such achievement of CNS Milestone [***] was by an Indication within [***]);

(e) If at the time of achievement of CNS Milestones [***] (or a requirement to pay the corresponding payment under this **Section 7.2.3**), a milestone payment corresponding to achievement of CNS Milestones [***]was not paid, then upon such achievement (or deemed achievement) of CNS Milestones [***], a milestone corresponding to such unpaid CNS Milestones [***] shall also become due and payable to Denali (except that CNS Milestone [***] would not be payable if such achievement of CNS Milestone [***] was by an Indication within [***]);

(f) If at the time of achievement of CNS Milestones [***] (or a requirement to pay the corresponding payment under this **Section 7.2.3**), a milestone payment corresponding to achievement of CNS Milestone [***] was not paid, then upon such achievement (or deemed achievement) of CNS Milestones [***], a milestone corresponding to such unpaid CNS Milestone [***] shall also become due and payable to Denali; and

(g) If at the time of receipt of the first Regulatory Approval by the FDA or EMA, whichever occurs first, for a CNS Product for an Indication within [***], a milestone payment corresponding to [***] involving a CNS Product for an Indication within [***] was not paid pursuant to **Section 7.2.2** ([***]), then, upon such receipt of first Regulatory Approval for a CNS Product for an Indication within [***], a milestone corresponding to such unpaid [***] milestone shall also become due and payable to Denali.

7.2.4 CNS Milestones Payable Once; Maximum Amount. For clarity, each CNS Milestone is payable only once, no CNS Milestones would be payable for subsequent or repeated achievements of milestone events with respect to one or more of the same or different CNS Products, and in no event would CNS Milestone Payments under this **Section 7.2** (CNS Program Milestones) with respect to CNS Products exceed Six Hundred Million Dollars ($600,000,000) in the aggregate ([***]).

7.2.5 Distinct and Different Indications. For purposes of determining whether a milestone event has been achieved under **Section 7.2** (CNS Program Milestone) or **Section 7.3** (Peripheral Program Milestones), (a) an Indication shall only be deemed a "**Distinct Indication**" if such disease or condition has [***], and (b) an Indication shall be deemed to be "**Different**" [***]. For the avoidance of doubt, [***].

7.2.6 Acceleration of First Approval Milestones. Upon [***] shall be due and payable by Sanofi to Denali upon Sanofi's receipt of an invoice therefor from Denali. If such payment occurs, the CNS Milestone Payment for [***].

7.3 Peripheral Program Milestones.

7.3.1 Peripheral Milestones. Sanofi shall pay to Denali, in accordance with **Section 7.4.2** (Reports and Payments for Milestones) and **Section 7.9** (Mode of Payment), the milestone payments set forth below ("**Peripheral Milestone Payments**") following the [***] of each of the following development, regulatory and sales milestone events (each, a "**Peripheral Milestone**" as numbered in the following table) with respect to a Peripheral Licensed Product (subject to **Section 7.4** (Other Matters Regarding Milestones)):

Peripheral Milestone	Peripheral Milestone Payment
1. [***]	[***]
2. [***]	[***]
3. [***]	[***]
4. [***]	[***]
5. [***]	[***]
6. [***]	[***]
7. [***]	[***]
8. [***]	[***]
9. [***]	[***]
10. [***]	[***]
11. [***]	[***]
12. [***]	[***]
13. [***]	[***]
14. [***]	[***]
15. [***]	[***]
16. [***]	[***]
17. [***]	[***]
18. [***]	[***]
19. [***]	[***]

7.3.2 Additional Peripheral Milestone Details. For purposes of **Section 7.3.1** (Peripheral Milestones):

(a) The Peripheral Licensed Product for the purposes of Peripheral Milestones [***] in the table in **Section 7.3.1** (Peripheral Milestones) may, but need not, be the same Peripheral Licensed Product;

(b) If, at the time of achievement of Peripheral Milestone [***] (or a requirement to pay the corresponding payment under this **Section 7.3.2**), a milestone payment corresponding to achievement of Peripheral Milestone [***] was not paid, upon such achievement (or deemed achievement) of Peripheral Milestone [***], a milestone corresponding to such unpaid Peripheral Milestone [***] shall also become due and payable to Denali;

(c) If, at the time of achievement of Peripheral Milestone [***] (or a requirement to pay the corresponding payment under this **Section 7.3.2**), a milestone payment corresponding to achievement of Peripheral Milestones [***] was not paid, upon such achievement (or deemed achievement) of Peripheral Milestone [***], a milestone corresponding to such unpaid Peripheral Milestones [***] shall also become due and payable to Denali;

(d) If, at the time of achievement of Peripheral Milestones [***] (or a requirement to pay the corresponding payment under this **Section 7.3.2**), a milestone payment corresponding to achievement of Peripheral Milestones [***] was not paid, upon such achievement

(or deemed achievement) of Peripheral Milestones [***], a milestone corresponding to such unpaid Peripheral Milestones [***] shall also become due and payable to Denali;

(e) If at the time of achievement of Peripheral Milestone [***], (or a requirement to pay the corresponding payment under this **Section 7.3.2**), a milestone payment corresponding to achievement of Peripheral Milestone [***] was not paid, upon such achievement (or deemed achievement) of Peripheral Milestone [***] then a milestone corresponding to such unpaid Peripheral Milestone [***] shall also become due and payable to Denali;

(f) If at the time of achievement of Peripheral Milestones [***] (or a requirement to pay the corresponding payment under this **Section 7.3.2**), a milestone payment corresponding to achievement of Peripheral Milestones [***] was not paid, upon such achievement (or deemed achievement) of Peripheral Milestones [***], a milestone corresponding to such unpaid Peripheral Milestones [***] shall also become due and payable to Denali;

(g) If at the time of achievement of Peripheral Milestone [***], (or a requirement to pay the corresponding payment under this **Section 7.3.2**), a milestone payment corresponding to achievement of Peripheral Milestone [***] was not paid, upon such achievement (or deemed achievement) of Peripheral Milestone [***], a milestone corresponding to such unpaid Peripheral Milestone [***] shall also become due and payable to Denali;

(h) If at the time of achievement of Peripheral Milestones [***] (or a requirement to pay the corresponding payment under this **Section 7.3.2**), a milestone payment corresponding to achievement of Peripheral Milestones [***] was not paid, upon such achievement (or deemed achievement) of Peripheral Milestones [***], a milestone corresponding to such unpaid Peripheral Milestone [***] shall also become due and payable to Denali.

7.3.3 Peripheral Milestones Payable Once; Maximum Amount. For clarity, each Peripheral Milestone is payable only once, no Peripheral Milestones would be payable for subsequent or repeated achievements of milestone events with respect to one or more of the same or different Peripheral Products, and in no event would Peripheral Milestone Payments under this **Section 7.3** (Peripheral Program Milestones) with respect to Peripheral Licensed Products exceed Four Hundred Ninety Five Million Dollars ($495,000,000) in the aggregate.

7.4 Other Matters Regarding Milestones.

7.4.1 Milestones on CNS Products Developed for Non-Neurology Indications and Peripheral Products Developed for Neurology Indications. Notwithstanding **Section 7.2.1** (CNS Milestones) and **Section 7.3.1** (Peripheral Milestones), but subject to **Section 7.2.6** (Acceleration of First Approval Milestones), if a CNS Product is Developed under this Agreement for any Indication(s) outside the Neurology Field (an "**Expanded Indication CNS Product**") or a Peripheral Product is Developed under this Agreement for any Indication(s) within the Neurology Field (an "**Expanded Indication Peripheral Product**"), then, Sanofi's obligation to pay milestones to Denali shall be as follows:

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(a) A milestone payment shall be due if a milestone payment would have been payable by Sanofi to Denali with respect to the applicable [***], disregarding for such purposes whether (i) the applicable Product is a CNS Product or a Peripheral Product, and (ii) the Indication to which [***] pertains is within, or outside of, the Neurology Field (but, for the avoidance of doubt, those milestone payments specific to [***] and set forth in **Section 7.2.2** ([***]) shall remain specific to [***] as set forth therein).

(b) With respect to an Expanded Indication CNS Product, if as a result of the assessment pursuant to clause (a) above, a milestone payment is so due from Sanofi to Denali, the amount of the corresponding milestone payment shall be based [***] until a payment has been made, pursuant to this **Section 7.4.1** or otherwise, with respect to all CNS Milestones and Peripheral Milestones that may trigger an obligation for Sanofi to make a payment to Denali with respect to the applicable [***] under **Section 7.2.1** (CNS Milestones) and **Section 7.3.1** (Peripheral Milestones) (taken together).

(c) With respect to an Expanded Indication Peripheral Product, if as a result of the assessment pursuant to clause (a) above, a milestone payment is so due from Sanofi to Denali, the amount of the corresponding milestone payment shall be based upon [***] until a payment has been made, pursuant to this **Section 7.4.1** or otherwise, with respect to all Peripheral Milestones and CNS Milestones that may trigger an obligation for Sanofi to make a payment to Denali with respect to the applicable [***] under Section 7.2.1 (CNS Milestones) and Section 7.3.1 (Peripheral Milestones) (taken together).

For clarity, nothing in this **Section 7.4.1** shall be deemed to require Sanofi to pay to Denali under this Agreement: (x) CNS Milestone Payments with respect to [***]; nor (y) Peripheral Milestone Payments with respect to [***]. Further, **Section 7.2.4** (CNS Milestones Payable Once; Maximum Amount) and **Section 7.3.3** (Peripheral Milestones Payable Once; Maximum Amount) shall remain in effect and nothing in this **Section 7.4.1** shall be deemed to require Sanofi to pay to Denali under this Agreement milestone payments of more than One Billion and Ninety-Five Million Dollars ($1,095,000) ([***]) if no additional payment is triggered under **Section 7.2.2** ([***])). Examples of milestone payment obligations for CNS Products Developed for Non-Neurology and Neurology Indications are provided in **Schedule 7.4.1(a)**. Examples of milestone payment obligations for Peripheral Products Developed for Non-Neurology and Neurology Indications are provided in **Schedule 7.4.1(b)**.

7.4.2 Reports and Payments for Milestones. With respect to each CNS Milestone set out in **Section 7.2** (CNS Program Milestones) and each Peripheral Milestone other than Peripheral Milestones [***] set out in **Section 7.3** (Peripheral Program Milestones), the Party who achieves such CNS Milestone or Peripheral Milestone, as applicable (or under whose authority such CNS Milestone or Peripheral Milestone, as applicable, is achieved), shall notify the other Party in writing within [***] after the achievement thereof. If Denali notifies Sanofi of such milestone event, Denali shall include an invoice for the corresponding milestone payment with such notice. If Sanofi notifies Denali of such milestone event, Denali shall promptly, after receipt of such notice, submit an invoice to Sanofi for the corresponding milestone amount. Sanofi shall pay to Denali the corresponding milestone payment set out in **Section 7.2** (CNS Program Milestones) or

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Section 7.3 (Peripheral Program Milestones), as applicable, no later than [***] after receipt of the applicable invoice. Each milestone payment set forth in **Section 7.2** (CNS Program Milestones) or **Section 7.3** (Peripheral Program Milestones) shall not be refundable and shall not be creditable against future milestone payments or other amounts paid or payable by Sanofi to Denali under this Agreement.

7.5 Royalties. Sanofi shall make the following royalty payments to Denali for sales of the relevant Products:

7.5.1 CNS Program. Subject to **Section 7.7** (Cost Profit Sharing) and **Section 7.8** (Denali Royalty Option), Sanofi shall pay to Denali royalties at the applicable royalty rates specified in the table below on the Net Sales of CNS Products in the Territory (excluding Net Sales of Cost Profit Sharing Products in the applicable Co-Commercialization Countries).

Tiered Annual CNS Net Sales	Royalty Rate
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]

7.5.2 Peripheral Program.

(a) **Peripheral Licensed Products**. Subject to **Section 7.5.2(b)** (Peripheral Products in the Neurology Field), Sanofi shall pay to Denali royalties at the applicable royalty rates specified in the table below on the Net Sales of Peripheral Licensed Products in the Territory.

Tiered Annual Worldwide Peripheral Net Sales	Royalty Rate
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]

(b) **Peripheral Products in the Neurology Field**. If the [***], then each of the royalty rates set forth in **Section 7.5.2(a)** (Peripheral Licensed Products) shall be increased by [***].

7.5.3 Royalty Term.

(a) **Duration of Accruals; Paid-Up**. Royalties under this **Section 7.5** (Royalties) shall be payable on a country-by-country basis and Product-by-Product basis beginning upon the First Commercial Sale of the applicable Product in such country until the expiration of the Royalty Term in such country. Upon completion of all such payments with respect to a Product in a country and all milestone payments or, if applicable, share of Net Revenues (if the Product was previously a Cost Profit Sharing Product), the licenses granted by Denali to Sanofi for such Product

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in such country shall be deemed fully paid-up, irrevocable, perpetual, non-terminable, and exclusive and survive termination of this Agreement in whole or in part for any reason ("**Fully Paid-Up License**").

(b) **Definitions**. For purposes of this **Section 7.5** (Royalties),

(i) "**Royalty Term**" means, with respect to a country and Product, the period commencing on the First Commercial Sale of such Product in such country and ending upon the later of: [***]; and

(ii) "**Royalty Term Determining Product Patent**" means: [***]; in every such case [***].

7.5.4 Royalty Reductions.

(a) **Patent Coverage**. If, during the Royalty Term for a Product, there does not exist in a given country [***] for so long as there are no such [***], such Product in such country at the time of the applicable Product sale.

(b) **Generic Competition**. On a Product-by-Product and country-by-country basis, if a Generic Version of such Product is launched in such country in a Calendar Quarter and Net Sales of such Product in such country decline by the percentage described below, relative to the average Net Sales of such Product in such country in the [***] Calendar Quarters prior to the first entry of such Generic Version in such country, then Sanofi's royalty payment obligations for Net Sales of such Product in such country for such Calendar Quarter and all future Calendar Quarters in which Net Sales of such Product in such country remain at or below such levels, will equal the following percentage of the otherwise applicable royalty rate pursuant to **Section 7.5.1** (CNS Program) or **Section 7.5.2** (Peripheral Program), as applicable, and **Section 7.5.4(a)** (Patent Coverage):

Decline in Net Sales	**Royalty Reduction**
[***]	[***]
[***]	[***]
[***]	[***]

(c) **In-License Agreements**.

(i) **Peripheral Program**. On a country-by-country basis and Peripheral Product-by-Peripheral Product basis, the royalties otherwise payable to Denali under this **Section 7.5** (Royalties) with respect to a Peripheral Product are subject to an offset by [***] of the royalties paid by Sanofi with respect to New Peripheral Program Technology that is [***]. Such amount(s) may be offset, in each case, up to a maximum amount of [***] of the royalty otherwise due to Denali with respect to Peripheral Products in the applicable Calendar Quarter, *provided* that any amounts that cannot be offset against amounts due to Denali by reason of the

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foregoing maximum amount shall be carried over into one or more subsequent Calendar Quarter(s) until the full offset is taken.

(ii) **CNS Program**. On a country-by-country basis and CNS Product-by-CNS Product basis, the royalties otherwise payable to Denali under this **Section 7.5** (Royalties) with respect to a CNS Product would be subject to an offset by [***] of the royalties paid by Sanofi with respect to New CNS Program Technology that is [***]. Such amount(s) may be offset, in each case, up to a maximum amount of [***] of the royalty otherwise due to Denali with respect to CNS Products in the applicable Calendar Quarter, *provided* that any amounts that cannot be offset against amounts due to Denali by reason of the foregoing maximum amount shall be carried over into one or more subsequent Calendar Quarter(s) until the full offset is taken.

(iii) [***]. Sanofi shall be responsible for the following amounts paid to [***] under the [***] with respect to a Compound or Product: [***] of all [***] (as defined in the [***]), milestone payments and royalties to the extent paid to [***] with respect to a [***] (as defined in the [***]). To the extent that the [***] is terminated and Sanofi receives the [***] or enters into a [***] agreement with [***] in accordance with that certain [***] between [***] dated [***] ("[***]" and any terms used in this **Section 7.5.4(c)(iii)** and not defined in this Agreement shall have the meaning given to such terms in the [***]), then Denali shall reimburse Sanofi for the following amounts paid to [***] in accordance with the [***]: [***] of all [***] (as defined in the [***]),[***] to the extent paid by Sanofi to [***] with respect to a [***] (as defined in the [***]) and [***] of amounts to the extent paid by Sanofi to [***] with respect to [***] (as defined in the [***]). Accordingly, a Party shall promptly reimburse the other Party who made the relevant payments to [***] under the [***] or as contemplated in the [***] for such first Party's share of such amounts as provided in this **Section 7.5.4(c)(iii)** within [***] of receipt of an invoice (or other written request) from the other Party with respect thereto, except that to the extent amounts paid to [***] under the [***] or as contemplated in the [***] are specifically allocable to a Cost Profit Sharing Product in a Cost Profit Sharing Country, such amounts shall be included in Allowable Expenses.

7.5.5 Manner of Royalty Payments. Within [***] following the end of each Calendar Quarter after the First Commercial Sale of a Product in the Territory, Sanofi shall provide to Denali a written, good-faith estimate, on a Product-by-Product basis, of Net Sales (in Euros) of such Product in the Territory during the preceding Calendar Quarter and the royalties payable by Sanofi to Denali pursuant to **Section 7.5.1** (CNS Program) and **Section 7.5.2** (Peripheral Program), as applicable. In addition, within [***] following the end of each Calendar Quarter after the First Commercial Sale of a Product in the Territory, Sanofi shall provide Denali with a written report ("**Quarterly Royalty Report**") detailing the following information for the applicable Calendar Quarter and on a Product-by-Product and country-by-country basis (to the extent applicable): [***], *provided, however*, that, [***]. Net Sales and royalties shall be presented in Euros in the Quarterly Royalty Report and converted into United States Dollars following the procedures set forth in **Section 7.9** (Mode of Payment). Within [***] following Denali's receipt of the Quarterly Royalty Report, Denali shall issue an invoice of the amount due, and Sanofi shall pay the full invoiced amount no later than [***] after Sanofi's receipt of such invoice.

7.6 Payments on Sanofi CNS Products and Sanofi Peripheral Products. For purposes of milestone and royalty payments owed pursuant to **Section 7.2** (CNS Program Milestones), **Section 7.3** (Peripheral Program Milestones), **Section 7.4.1** (Milestones on CNS Products Developed for Non-Neurology Indications and Peripheral Products Developed for Neurology Indications) and **Section 7.5** (Royalties), Sanofi CNS Products and Sanofi Peripheral Products shall be treated as CNS Licensed Products and Peripheral Licensed Products, respectively, in all respects except that the amount(s) payable to Denali with respect to Sanofi CNS Product and Sanofi Peripheral Products pursuant to **Section 7.2** (CNS Program Milestones), **Section 7.3** (Peripheral Program Milestones) and **Section 7.5** (Royalties), shall be [***] of the corresponding amount(s) payable with respect to CNS Licensed Products and Peripheral Licensed Products.

7.7 Cost Profit Sharing. Starting on the Effective Date, the Parties will share Shared Development Costs and Allowable Expenses and Net Revenues associated with each such CNS Product (for so long as, and solely with respect to the country for which, such Cost Profit Sharing is in effect, a "**Cost Profit Sharing Product**") on a country-by-country basis in each of the United States and China (each, a "**Cost Profit Sharing Country**") as provided in, and subject to the terms of, this **Section 7.7** (such cost profit sharing arrangement, "**Cost Profit Sharing**"). The Parties will share Shared Development Costs for the CNS Program for all other countries of the Territory subject to the terms set forth in this **Section 7.7**. The Parties will not share Allowable Expenses and Net Revenues for the CNS Program for any other countries of the Territory; all such other countries are subject to the payment of royalties pursuant to **Section 7.5.1** (CNS Program); nor will the Parties share any Development Costs or costs incurred in the Manufacture or Commercialization of any Peripheral Products.

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7.7.1 Sharing Percentages. Denali and Sanofi shall be responsible for their respective portions of Development Costs, Shared Development Costs, Allowable Expenses and Net Revenues at the percentages set forth in the table below in accordance with the terms set forth in this **Section 7.7** (Cost Profit Sharing).

Category	Denali	Sanofi
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]

7.7.2 Excess Development Cost Sharing Procedures.

(a) Notwithstanding the other provisions of this **Section 7.7** (Cost Profit Sharing), with respect to each Initial CNS Phase III Trial and any other Phase III Trial for a CNS Product (including any associated Safety Study) that Denali agrees to include in the CNS Development Plan, if [***]. Denali shall provide the foregoing notice to Sanofi no later than [***] after the end of any Calendar Quarter in which [***].

(b) If Denali delivers to Sanofi an [***] in accordance with the time periods in **Section 7.7.2(a)**, then (x) Sanofi shall be responsible for [***]. Denali shall only be entitled to make the election provided in foregoing clauses (A) and (B) of the preceding sentence during the following time periods, to the extent applicable: (xx) before the start of the Launch Window for a CNS Product that is the subject of a First Co-Commercialization Drug Approval Application in a country within the Co-Commercialization Territory, if Denali is not then conducting any Co-Commercialization Activities in such country; and (yy) within [***] after Sanofi obtains Regulatory Approval for the CNS Product if (1) the relevant Drug Approval Application constituted a First Co-Commercialization Drug Approval Application in a country within the Co-Commercialization Territory and Denali is conducting any Co-Commercialization Activities in such country, (2) the applicable Regulatory Approval did not result from a First Co-Commercialization Drug Approval Application in a country within the Co-Commercialization Territory or was obtained in [***]. If Denali provides Sanofi with a timely [***], then Denali shall pay to Sanofi the applicable [***] within [***] after Regulatory Approval of the subject CNS Product is obtained. If Denali does not provide Sanofi with an [***], Denali shall not have any obligation to pay to Sanofi any of the applicable [***], and Sanofi shall not have the right to offset or credit such amounts against any payments to Denali under this Agreement. [***].

(c) For each Initial CNS Phase III Trial or any other Phase III Trial (including the Shared LTS Costs for any associated Safety Study) for a CNS Product that Denali agrees to include in the CNS Development Plan, the applicable "**Cost Cap**" shall be:

(i) in the case of an Initial CNS Phase III Trial (including the Shared LTS Costs for any associated Safety Study), an amount that is the lesser of: (x) the sum of (A) [***], and (B) [***]; and (y) [***], and (B) [***]; and

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(ii) in the case of any other Phase III Trial (including any Shared LTS Costs for any associated Safety Study) for a CNS Product that Denali agrees to include in the CNS Development Plan, the sum of (A) [***]; and (B) [***].

7.7.3 Shared Development Costs and Allowable Expenses.

(a) **General**. Within [***], unless such timing is adjusted by the Finance Working Group, prior to the end of each [***], each Party will provide the other Party with a good-faith estimate of the Shared Development Costs and Allowable Expenses it incurred in such [***] for each Cost Profit Sharing Product in each applicable Cost Profit Sharing Country. The Finance Working Group will establish the level of detail necessary in such estimate for each Party to satisfy its internal reporting requirements. No later than [***] prior to the end of each Calendar Quarter, unless such timing is adjusted by the Financial Working Group, each Party will provide the other Party with a reasonably detailed estimate of the Shared Development Costs and Allowable Expenses it incurred in such Calendar Quarter for each Cost Profit Sharing Product in each applicable Cost Profit Sharing Country, which will include the actual costs for the first two [***] and good-faith estimate for the last [***]. Within [***] after the end of each Calendar Quarter, unless such timing is adjusted by the Financial Working Group, each Party will provide the other Party with a report of actual Shared Development Costs and Allowable Expenses for such Calendar Quarter for each Cost Profit Sharing Product in each applicable Cost Profit Sharing Country and, to the extent applicable, the cumulative amount of any Excess Study Costs (if applicable), which report will contain a detailed and itemized calculation of such costs for each Cost Profit Sharing Product. In addition to the annual approval of the relevant budgets for the CNS Program by the JSC, at the frequency of [***], and prior to the end of June and October of each Calendar Year, each Party will provide the Finance Working Group with a non-binding estimate of its Shared Development Costs, Excess Study Costs (if applicable) and Allowable Expenses for each Cost Profit Sharing Product in each applicable Cost Profit Sharing Country for the [***] period [***] following the first Calendar Year covered by such approved budget; *provided* that the Parties will review and discuss such estimated costs at the Finance Working Group or the JCC.

(b) **Expense Review**. Each Party shall have the right to review and submit any reasonable objection to the Shared Development Costs, Excess Study Costs (if applicable) or Allowable Expenses set forth in the other Party's report within [***] following its receipt of the applicable report from the other Party. Without limiting a Party's rights under **Section 7.14** (Audit), if a Party fails to object to a Shared Development Cost, Excess Study Costs (if applicable) or Allowable Expense submitted by the other Party within such [***] period, such Shared Development Cost or Allowable Expense shall be deemed accepted by such Party. If a Party exercises its right under **Section 7.14** (Audit), the audit findings shall prevail. If a Party requests supporting documentation for any Shared Development Costs, Excess Study Costs (if applicable) or Allowable Expenses set forth in the other Party's report, such Party shall promptly (and in any event within [***]) provide such documentation to the requesting Party as may be reasonably necessary to allow the requesting Party to understand the applicable Shared Development Costs, Excess Study Costs (if applicable) or Allowable Expenses. Any dispute as to respect to a Shared Development Cost, Excess Study Costs (if applicable) or Allowable Expense shall be resolved by the Finance Working Group in accordance with **Section 7.7.9** (Cost Profit Sharing Disputes).

7.7.4 Net Sales and Net Revenues. In order to satisfy each Party's internal reporting requirements, within [***], unless such timing is adjusted by the Finance Working Group, after the end of each [***], Sanofi will provide Denali with a good-faith estimate of Net Sales and Net Revenues for each Cost Profit Sharing Product for such [***] allocable to each Cost Profit Sharing Country. The Finance Working Group will establish the level of detail necessary in such estimate for each Party to satisfy its internal reporting requirements and reporting requirements pursuant to its applicable Accounting Standards. Within [***] after the end of each Calendar Quarter, unless such timing is adjusted by the Finance Working Group, Sanofi will provide Denali with a reasonably detailed estimate of such Net Sales and Net Revenues for such Calendar Quarter allocable to each country, which will include the actual Net Sales and Net Revenues for the first [***] and a good-faith estimate for the last [***] allocable to each Cost Profit Sharing Country. Within [***] after the end of each Calendar Quarter, unless such timing is adjusted by approval of the JSC, Sanofi will provide Denali with a report of such Net Sales and Net Revenue for such Calendar Quarter allocable to each country, [***].

7.7.5 Reporting, Reconciliation and True-Up. Within [***] after the end of each Calendar Quarter, Sanofi will calculate and provide to each Party and the Finance Working Group a report of, and an invoice for, the amount each Party is responsible for under **Section 7.7** (Cost Profit Sharing) with respect to the CNS Program, such that the Parties share Shared Development Costs, Allowable Expenses, and all Net Revenues, for such Calendar Quarter, in accordance with the percentages set forth in **Section 7.7.1** (Sharing Percentages). One of the Parties will make a balancing payment ("**Balancing Payment**") to the other Party in order to cause such sharing as set forth in **Section 7.7** (Cost Profit Sharing) within [***] after the issuance of the report by Sanofi under this **Section 7.7.5**.

7.7.6 Certain Other Matters Relating to Cost Calculations.

(a) **Allocation of FTE Costs and Out-of-Pocket Costs**. It is understood that Shared Development Costs and Allowable Expenses shall (i) [***]; and (ii) [***]. To the extent that any activity is conducted (or an Out-of-Pocket Cost or FTE Cost is incurred) is not solely attributable to actual Shared Development Costs or Allowable Expenses for a Cost Profit Sharing Product in a Cost Profit Sharing Country (including, for example and not by way of limitation, Manufacturing Costs incurred with respect to the scale up of Manufacturing activities for a particular Cost Profit Sharing Product), then such Out-of-Pocket Costs, FTE Costs or other costs for the applicable activity shall be included in Shared Development Costs and Allowable Expenses only to the extent fairly and reasonably allocated to Shared Development Costs or Allowable Expenses for a Cost Profit Sharing Product in the applicable Cost Profit Sharing Country, in each case in accordance with Accounting Standards. [***].

(a) **Treatment of Overhead; Other Matters**. The Parties acknowledge and agree that Development Costs and Allowable Expenses shall not include allocation of overhead [***]. Except to the extent already included [***], Development Costs and Allowable Expenses shall not include either Party's costs to the extent pertaining to [***] activities associated with overseeing execution of and compliance with this Agreement, unless otherwise agreed by the Parties under this Agreement or otherwise in writing. Development Costs and Allowable Expenses

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shall also exclude: (i) any costs attributable to a breach of this Agreement by either Party; or (ii) Indemnified Losses subject to indemnification pursuant to **Section 12.1** (Indemnification of Denali) or **Section 12.2** (Indemnification of Sanofi), except as otherwise expressly provided in **Section 1.6** ("Allowable Expenses" definition), **Section 1.44** ("Development Costs" definition) or **Section 1.143** ("Shared Development Costs" definition), .

7.7.7 Financial Reporting Activities; Finance Working Group. With respect to the financial reporting activities between the Parties, unless Denali has exercised the Denali Royalty Option pursuant to **Section 7.8** (Denali Royalty Option), the JSC shall establish a finance working group ("**Finance Working Group**") to coordinate the activities and reporting by the Parties as set forth in **Section 7.7.3** (Shared Development Costs and Allowable Expenses) and to assist the JSC in its responsibilities with respect to the review and resolution of financial matters. In particular, the Finance Working Group shall:

(a) facilitate the creation of CNS Development Budget and Co-Commercialization Budget, including the annual updates thereto;

(b) reconcile financial and accounting matters between the Parties;

(c) initiate and execute an effective and efficient revenue and cost sharing process (cross-charges);

(d) cooperate to ensure that the CNS Development Budget and Co-Commercialization Budget agreed to for a Calendar Year (or any other given period) can be interpreted for the purposes of both Parties' internal financial and audit reporting requirements, including each Party's fiscal year reporting;

(e) monitor the budget, expense and revenue reporting requirements between the Parties related to the Programs to ensure that each Party is able to comply with its respective internal financial and audit reporting requirements and, as appropriate, recommending to the JSC for approval, changes to the reporting requirements under this Agreement; and

(f) undertake such other tasks with respect to the calculation, implementation and reporting for the Parties' sharing of Manufacturing Costs, Shared Development Costs, Allowable Expenses and Net Revenues as the Parties mutually agree.

7.7.8 Consequences of Non-Compliance with Cost Sharing Obligations. In the event that [***] (*provided* that, if [***], which shall [***]; *provided, however*, that, [***]. For the avoidance of doubt, [***].

7.7.9 Cost Profit Sharing Disputes. [***]. In the event [***].

7.7.10 [***]. With respect to each Cost Profit Sharing Product in a Cost Profit Sharing Country, if (a) [***], and (c) [***], then, [***] in such Cost Profit Sharing Product in a Cost Profit Sharing Country [***] in a [***] conducted in accordance with the following terms:

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(a) [***]. Promptly following [***] delivery of the [***], the Parties will engage in [***] of the [***] and, if the Parties are unable to mutually agree [***] will occur within [***] after the [***],[***] shall be entitled to [***] by submitting [***] (a) [***], and (b) [***].

(b) **Invoices**. Following receipt of the [***], if applicable, [***] will send to [***] an invoice for the amount determined in accordance with **Section 7.7.10(a)** ([***]) to be payable at the [***].

(c) **Closing**. If the [***] occurs, the Parties will select [***], which [***] shall not be earlier than [***], nor later than [***], from the [***]. At such [***],[***] will pay the amount invoiced pursuant to **Section 7.7.10(b)** (Invoices), if any, in immediately available funds. Effective as of the [***], the Agreement with respect to the applicable Cost Profit Sharing Product in the Cost Profit Sharing Country [***].

7.8 Denali Royalty Option (to Stop Cost Profit Sharing).

7.8.1 Exercise by Denali. Denali may, upon [***] prior written notice to Sanofi or as otherwise provided in **Section 7.7.2** (Excess Development Cost Sharing Procedures), opt out of future Cost Profit Sharing with respect to each Cost Profit Sharing Product (and any other CNS Products including the same CNS Compound as such Cost Profit Sharing Product), and any Excess Study Costs with respect to such CNS Product in one or both Cost Profit Sharing Country(ies) incurred pursuant to **Section 7.7** (Cost Profit Sharing), such option, the "**Denali Royalty Option**". Each Cost Profit Sharing Product with respect to which Denali exercises the Denali Royalty Option (and all other CNS Products including the same CNS Compound as any such Cost Profit Sharing Product) may be referred to as a "**Cost Profit Sharing Opt Out Products**") and each corresponding country may be referred to as a "**Cost Profit Sharing Opt Out Country**". The end of the [***] period specified in Denali's notice is referred to in this Agreement as the "**Co-Funding End Date**".

7.8.2 Consequences of Exercise of Denali Royalty Option on Payments. Effective from and after the Co-Funding End Date, Denali shall not be obligated or allowed to share Allowable Expenses or Net Revenues for the applicable Cost Profit Sharing Opt Out Product in the applicable Cost Profit Sharing Opt Out Country or Shared Development Costs for the Cost Profit Sharing Opt Out Product and Sanofi shall begin accruing royalties for the subject Cost Profit Sharing Opt Out Product in the corresponding Cost Profit Sharing Opt Out Country(ies) in accordance with the royalty rates set forth below. Following each exercise or election of the Denali Royalty Option with respect to a Cost Profit Sharing Product, the royalty rate applicable to such corresponding Cost Profit Sharing Opt Out Product for each tier set forth in the table in **Section 7.5.1** (CNS Program) shall be increased as set forth in the table below, determined on the basis of the total amount of Development Costs (including Additional CNS Development Costs to the extent such amounts are included in the CNS Development Budget pursuant to **Section 3.2.4(e)** (Opt In for Additional CNS Development Activities)), and any Excess Cost Opt-In Amount that Denali elects to pay in accordance with **Section 7.7.2** (Excess Development Cost Sharing Procedures) and any amount that Denali elects to pay in accordance with **Section 3.2.4** (Additional CNS Program Development Activities) with respect to Additional CNS Development Activities conducted by Sanofi) that have

been borne by Denali with respect to all Cost Profit Sharing Opt Out Products at the time of such exercise or election ("**Co-Funding Amount**"):

Co-Funding Amount	Royalty Rate Adjustment
[***]	[***]
[***]	[***]
[***]	[***]

[***], the applicable royalty rates on Annual CNS Net Sales for such Cost Profit Sharing Product applicable from and after the Co-Funding End Date following such exercise Denali Royalty Option, shall be as follows:

Tiered Annual CNS Net Sales	Royalty Rate
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]

7.8.3 Other Consequences of Exercise of Denali Royalty Option. Notwithstanding anything to the contrary in **Article 1** (Definitions), **Article 2** (Collaboration Management), **Article 3** (Development and Regulatory Activities), **Article 4** (Manufacturing) or **Article 5** (Commercialization), in the event Denali exercises the Denali Royalty Option pursuant to this **Section 7.8** (Denali Royalty Option), the following shall also apply from and after the Co-Funding End Date with respect to the applicable Cost Profit Sharing Opt Out Products and Cost Profit Sharing Opt Out Country:

(a) **No Longer a Cost Sharing Product**. The Cost Profit Sharing Opt Out Product shall no longer be deemed a Cost Profit Sharing Product in the corresponding Cost Profit Sharing Opt Out Country(ies) that was/were the subject of the Denali Royalty Option, and such Cost Profit Sharing Opt Out Country(ies) shall no longer be deemed Cost Profit Sharing Country(ies) with respect to such Cost Profit Sharing Opt Out Products.

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(b) **Sanofi Development and Regulatory Lead**. Notwithstanding **Section 3.2.3(d)** (Designation of Development Lead for the CNS Program) and **Section 3.4.2** (CNS Program Regulatory Lead), Sanofi shall be designated the Development Lead and Regulatory Lead for the Cost Profit Sharing Opt Out Product in the corresponding Cost Profit Sharing Opt Out Country(ies).

(c) **Plans**. Without limiting Sanofi's obligations under **Section 3.2.2** (Amendments and Updates), **Section 5.2.5** (Commercialization Reports) or **Section 5.3.3** (Amendments and Updates), on at least an annual basis thereafter, Sanofi shall submit (i) a revised CNS Development Plan to the JSC for review and comment, and (ii) a Global Commercialization Plan (if appropriate based on the then-current Development stage of the Products) to the JSC for review and comment that includes the Cost Profit Sharing Opt Out Product in the corresponding Cost Profit Sharing Opt Out Country(ies).

(d) **Sanofi Decision-Making**. Sanofi shall, notwithstanding **Section 2.4.5** (Joint Committee Decision Making), have the right to make decisions with respect to the Cost Profit Sharing Opt Out Product in the corresponding Cost Profit Sharing Opt Out Country(ies) as if such CNS Product was a Peripheral Product.

(e) **JDC and JCC Meetings**. If Denali exercises the Denali Royalty Option pursuant to this **Section 7.8** (Denali Royalty Option) for all Cost Profit Sharing Products in both Cost Profit Sharing Countries, the JDC and JCC shall no longer meet after the second (2^{nd}) anniversary of the First Commercial Sale of the first CNS Product. Thereafter, Sanofi shall provide Denali an annual update of all material Development and Commercialization activities in the Major Markets that were completed in the prior Calendar Year and those planned for the upcoming Calendar Year with respect to CNS Products.

7.9 Mode of Payment. All payments to either Party under this Agreement shall be made from a U.S. entity through a banking institution located in the United States by deposit of Dollars in the requisite amount to such bank account as the receiving Party may from time to time designate by notice to the paying Party. For the purpose of calculating any sums due under, or otherwise reimbursable pursuant to, this Agreement (including the calculation of Net Sales and royalties expressed in Euros), a Party shall convert any amount expressed in a foreign currency into Dollar equivalents in the manner used by such Party from time to time in the preparation of its audited financial statements for external reporting purposes (*provided* that such practices use one or more widely accepted sources of exchange rates) or an equivalent resource as agreed by the Parties, during the Calendar Quarter for which a payment is due.

7.10 Withholding Taxes.

7.10.1 Reductions. The amounts payable pursuant to this Agreement ("**Payments**") shall not be reduced on account of any Taxes, unless required by Applicable Law. A payor Party shall deduct and withhold from the Payments any Taxes that it is required by

Applicable Law to deduct or withhold. Notwithstanding the foregoing, the Parties shall use reasonable efforts to take all such acts and to sign all such documents as will enable them to take advantage of any applicable double taxation agreement or treaty, and if a recipient is entitled under any applicable tax treaty to a reduction of rate of, or the elimination of, or recovery of, applicable withholding tax, it may deliver to the payor Party or the appropriate governmental authority the prescribed forms necessary to reduce the applicable rate of withholding or to relieve the payor Party of its obligation to withhold tax. In such case, the payor Party shall apply the reduced rate of withholding, or not withhold, as the case may be, *provided* that the payor Party is in receipt of evidence (*e.g.*, the recipient's delivery of all applicable documentation), in a form reasonably satisfactory to the payor Party, at least [***] week prior to the time that the Payments are due. If, in accordance with the foregoing, the payor Party withholds any amount, it shall pay to the recipient Party the balance when due, make timely payment to the proper taxing authority of the withheld amount, and send the recipient Party proof of such payment within [***] following that payment.

7.10.2 Assignments. If a Party that owes a payment under this Agreement assigns its rights and obligations to any person as permitted in accordance with **Section 15.3** (Assignment; Effects of Acquisitions) and if, solely as a result of such assignment, the withholding or deduction of taxes required by Applicable Law with respect to payments owed by such assignee under this Agreement is increased, then any amount payable under this Agreement shall be increased to take into account such withheld or deducted taxes as may be necessary so that, after making all required tax withholdings and deductions (including tax withholdings and deductions on amounts payable under this **Section 7.10** (Withholding Taxes)), the payee receives an amount equal to the sum it would have received as of the Effective Date.

7.11 Indirect Taxes. All payments are exclusive of value added taxes, sales taxes, consumption taxes and other similar taxes ("**Indirect Taxes**"). If any Indirect Taxes are chargeable in respect of any payments, the paying Party shall pay such Indirect Taxes at the applicable rate in respect of such payments following receipt, where applicable, of an Indirect Taxes invoice in the appropriate form issued by the receiving Party in respect of those payments. The Parties shall issue invoices for all amounts payable under this Agreement consistent with Indirect Tax requirements and irrespective of whether the sums may be netted for settlement purposes. If the Indirect Taxes originally paid or otherwise borne by the paying Party are in whole or in part subsequently determined not to have been chargeable, all reasonably necessary steps requested by the paying Party will be taken by the receiving Party to receive a refund of these undue Indirect Taxes from the applicable governmental authority or other fiscal authority and any amount of undue Indirect Taxes repaid by such authority to the receiving Party (net of any amounts incurred with respect to the receipt of such amounts) will be transferred to the paying Party within [***] of receipt.

7.12 Interest on Late Payments. If any payment or portion thereof due to either Party under this Agreement is not paid when due, then such paying Party shall pay interest thereon at a rate equal to [***] or, if lower, the maximum rate permitted by Applicable Law, calculated on the number of days such payment is delinquent, compounded annually and computed on the basis of a three hundred and sixty-five (365) day year.

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7.13 Financial Records. Each Party shall keep complete and accurate books and records pertaining to Net Sales of Products, Additional CNS Development Costs, Shared Development Costs, Allowable Expenses and Net Revenues with respect to the CNS Compounds and CNS Products, and Development of the Compounds or Products, including books and records of actual expenditures with respect to the budgets set forth in the CNS Development Plan and the Co-Commercialization Plan, in sufficient detail to calculate all amounts payable hereunder and to verify compliance with its obligations under this Agreement. Such books and records shall be retained by such Party until the later of (a) [***] after the end of the period to which such books and records pertain, and (b) the expiration of the applicable tax statute of limitations (including any extensions thereof), or for such longer period as may be required by Applicable Law.

7.14 Audit. At the request of the other Party, each Party shall permit an independent public accounting firm of nationally recognized standing designated by the other Party and reasonably acceptable to the audited Party, at reasonable times during normal business hours and upon reasonable notice, to audit the books and records maintained pursuant to **Section 7.13** (Financial Records) to ensure the accuracy of all reports and payments made hereunder, *provided* that such rights with respect to records pertaining to Additional CNS Development Costs for an Additional CNS Development Activity shall not be exercised until after an Additional CNS Development Opt-In Notice is provided with respect to such Additional CNS Development Activity. Such examinations may not (a) be conducted for any Calendar Quarter more than [***] after the end of such quarter, (b) be conducted more than once in any [***] period (unless a previous audit during such [***] period revealed an underpayment with respect to such period) or (c) be repeated for any Calendar Quarter; except in each case, for cause. The accounting firm shall disclose to the auditing Party whether the reports are correct or not, and the details concerning any discrepancies sufficient for the auditing Party to understand any such discrepancies. Absent manifest error by such independent accounting firm, the determination of such independent accounting firm shall be binding on the Parties. Except as provided below, the cost of this audit shall be borne by the auditing Party, unless the audit reveals a variance of greater than [***] from the reported amounts for the inspected period, in which case the audited Party shall bear the cost of the audit. If such audit concludes that (i) additional amounts were owed by the audited Party, the audited Party shall pay the additional amounts, with interest from the date originally due as provided in **Section 7.12** (Interest on Late Payments), or (ii) excess payments were made by the audited Party, the auditing Party shall, at its election, reimburse such excess payments or elect that such excess payments shall be offset against future payments due to the auditing Party under this Agreement, in either case ((i) or (ii)), within [***] after the date on which such audit is completed by the auditing Party.

7.15 Confidentiality. The receiving Party shall treat all information subject to review under this **Article 7** (Payments) in accordance with the confidentiality provisions of **Article 10** (Confidentiality and Non-Disclosure) and the Parties shall enter into a reasonably acceptable confidentiality agreement with the independent accountant obligating such accountant to retain all such financial information in confidence pursuant to such confidentiality agreement.

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7.16 No Other Compensation. Each Party hereby agrees that the terms of this Agreement fully define all consideration, compensation and benefits, monetary or otherwise, to be paid, granted or delivered by a Party to the other Party in connection with the transactions contemplated herein. Neither Party previously has paid or entered into any other commitment to pay, whether orally or in writing, any of the other Party's employees, directly or indirectly, any consideration, compensation or benefits, monetary or otherwise, in connection with the transaction contemplated herein.

ARTICLE 8
INTELLECTUAL PROPERTY

8.1 Ownership of Intellectual Property.

8.1.1 Ownership of Patents and Know-How Generated under this Agreement. As between the Parties, [***].

8.1.2 Assignment, Disclosure and Assistance Obligation. Each Party shall cause all employees and contractors who perform activities for such Party or its Affiliate under this Agreement to be under an obligation to assign their rights in any Information, inventions, discoveries, improvements and works resulting therefrom to such Party or its Affiliate. At the request of [***] shall require its employees and contractors who are inventors on any such Program Patent to cooperate and provide assistance to its employer or its Affiliate in relevant intellectual property-related matters, including by executing all appropriate documents, cooperating in discovery and, if legally required to continue any such enforcement activities, joining as a party to any action or providing a power of attorney solely for such purpose. For clarity, the requirements of **Section 6.4** (Subcontracting) and **Section 15.15** (Performance by Affiliates, Sublicensees and Third Party Providers) shall apply to each Party's use of Third Party Providers, Affiliates or Sublicensees, to perform activities for such Party under this Agreement.

8.1.3 Ownership of Corporate Names. Each Party shall retain all right, title and interest in and to its Corporate Names.

8.2 Maintenance and Prosecution of Patents. As between the Parties, and subject to **Section 6.5.3** (Coordination with Third Party Agreements) and the requirements of the Existing In-License Agreements, with respect to [***], the following shall apply:

8.2.1 [***].

(a) [***]. [***].

(b) [***]. [***]s.

(c) [***]. [***].

(d) [***]. [***].

8.2.2 [***]. [***].

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8.2.3 [***]. [***].

8.2.4 [***]. [***].

8.2.5 [***]. [***].

8.3 [***]. [***]:

8.3.1 [***]. [***].

8.3.2 Infringement Enforcement Actions.

(a) [***]. [***].

(b) [***]. [***].

8.3.3 [***]. [***].

8.3.4 [***]. [***].

8.3.5 [***]. [***].

8.3.6 [***]. [***].

8.4 [***]. [***].

8.5 Invalidity or Unenforceability Defenses or Actions.

8.5.1 Notice. Each Party shall promptly notify the other Party in writing of any alleged or threatened assertion of invalidity or unenforceability of any of the Product Patents by a Third Party, in each case of which such Party becomes aware.

8.5.2 [***]. [***].

8.5.3 [***]. [***].

8.5.4 [***]. [***].

8.5.5 [***]. [***].

8.6 Product Trademarks.

8.6.1 [***]. [***].

8.6.2 [***]. [***].

8.6.3 [***]. [***].

8.6.4 [***]. [***].

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8.6.5 [***]. [***].

8.7 [***]. [***]:

8.7.1 [***]**.** [***].

8.7.2 [***]**.** [***].

8.7.3 [***]**.** [***].

8.8 [***]. [***].

ARTICLE 9
PHARMACOVIGILANCE AND SAFETY

9.1 Pharmacovigilance. Each Party shall provide the other Party with all Information reasonably necessary or desirable for such Party to comply with its pharmacovigilance responsibilities in all countries in the Territory. Sufficiently in advance of the start of any Clinical Trials conducted under this Agreement, the Parties shall enter into an agreement ("**Pharmacovigilance Agreement**") to initiate a process for the exchange of safety data (including post-marketing spontaneous reports received by each Party and its Affiliates) in a mutually agreed format in order to monitor the safety of the Compounds or Products and to meet reporting requirements with any applicable Regulatory Authority.

9.2 Global Safety Database.

9.2.1 CNS Program. Within [***] after the Effective Date, Denali shall initially set up, and thereafter will hold and maintain the global safety database for CNS Compounds and CNS Products with respect to safety data obtained in connection with the Denali CNS Development Activities. In connection with the commencement of Sanofi CNS Development Activities by Sanofi and in accordance with the Transition Plan, or if Denali exercises the Denali Royalty Option, Denali shall transfer to Sanofi, in the electronic format agreed upon by the Parties at the JDC, the complete contents of the safety database maintained by Denali pursuant to this **Section 9.2.1** for the CNS Compounds and CNS Products. Thereafter Sanofi shall maintain the global safety database for such CNS Compounds and CNS Products.

9.2.2 Peripheral Program. Sanofi shall maintain the global safety database for Peripheral Compounds and Peripheral Products.

9.2.3 Costs. Each Party's and its Affiliates' costs incurred in connection with receiving, recording, reviewing, communicating, reporting and responding to adverse events with respect to such Compounds and Products and in establishing and maintaining a global safety database for such Compounds and Products (a) shall be included in the Allowable Expenses to the extent pertaining to a Cost Profit Sharing Product in a Cost Profit Sharing Country; and (b) [***].

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9.3 Patient Safety Cooperation. Each Party agrees that ensuring patient safety is an essential aspect of the product development and commercialization process and, in furtherance thereof, each Party agrees to use reasonable efforts to cooperate with the other Party with respect to any patient safety matters arising under this Agreement, and will consider the other Party's views on safety matters reasonably and in good faith in light of each Party's interest in developing therapeutic solutions that comply with applicable regulatory, safety and ethical standards. Without limiting the foregoing, if either Party reasonably believes that the [***] is likely to identify a Patient Safety Risk that could reasonably affect [***] then such Party shall notify the other Party, and, at either Party's request, the Parties will discuss and consider in good faith [***]. Sanofi will ensure (through its JSC members or otherwise) that a presentation made by the relevant Sanofi personnel at a meeting of the [***] regarding any such matters will include (i) [***] and (ii) [***]. In addition, at Sanofi's sole discretion, Denali may directly participate in such a meeting of the [***].

ARTICLE 10
CONFIDENTIALITY AND NON-DISCLOSURE

10.1 Confidentiality Obligations. At all times during the Term and for a period of [***] following termination or expiration of this Agreement in its entirety, each Party shall, and shall cause its Affiliates and its and their respective officers, directors, employees and agents to, keep confidential and not publish or otherwise disclose to a Third Party and not use, directly or indirectly, for any purpose, any Confidential Information furnished or otherwise made known to it, directly or indirectly, by the other Party, except to the extent such disclosure or use is expressly permitted by the terms of this Agreement and is reasonably necessary or useful for the performance of such Party's obligations, or the exercise of rights expressly granted to such Party under, this Agreement. The terms, but not the mere existence, of this Agreement will also be considered Confidential Information for which each Party is a receiving Party for purposes of this **Article 10** (Confidentiality and Non-Disclosure).

10.2 Exceptions. Notwithstanding the foregoing, the confidentiality and non-use obligations under **Section 10.1** (Confidentiality Obligations) shall not apply to any information that the receiving Party can demonstrate by documentation or other competent proof:

10.2.1 has been published by a Third Party or otherwise is or becomes part of the public domain by public use, publication, general knowledge or the like through no wrongful act, fault or negligence on the part of the receiving Party;

10.2.2 is in the receiving Party's possession prior to disclosure by the disclosing Party, to the extent the receiving Party has the right to use and disclose such information;

10.2.3 is subsequently lawfully received by the receiving Party from a Third Party, to the extent the receiving Party has the right to use and disclose such information without breach of any agreement between such Third Party and the disclosing Party;

10.2.4 is published or otherwise generally made available to Third Parties by the disclosing Party without restriction on disclosure; or

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10.2.5 is independently developed by or for the receiving Party without reference to, or use or disclosure of, the disclosing Party's Confidential Information.

Specific aspects or details of Confidential Information shall not be deemed to be within the public domain or in the possession of the receiving Party merely because the Confidential Information is embraced by more general information in the public domain or in the possession of the receiving Party. Further, any combination of Confidential Information shall not be considered in the public domain or in the possession of the receiving Party merely because individual elements of such Confidential Information are in the public domain or in the possession of the receiving Party unless the combination is in the public domain or in the possession of the receiving Party.

10.3 Permitted Disclosures. Each Party may disclose Confidential Information to the extent that such disclosure is:

10.3.1 in the reasonable opinion of the receiving Party's legal counsel, required to be disclosed pursuant to law, regulation or a valid order of a court of competent jurisdiction or other supra-national, federal, national, regional, state, provincial and local governmental body of competent jurisdiction, (including by reason of filing with securities regulators, but subject to **Section 10.5** (Public Announcements)); *provided* that the receiving Party shall, unless otherwise prohibited, first have given advanced written notice (and to the extent possible, at least [***] notice) to the disclosing Party and (other than with regard to disclosures to securities regulators or to comply with applicable securities law, which disclosures are covered in **Section 10.5** (Public Announcements)) give the disclosing Party a reasonable opportunity to take whatever action it deems necessary to protect its Confidential Information via a protective order or confidential treatment request. In the event that no such protective order, confidential treatment, or other remedy is obtained, or the disclosing Party waives compliance with the terms of this Agreement, the receiving Party shall furnish only that portion of Confidential Information which the receiving Party is advised by counsel is legally required to be disclosed;

10.3.2 made by or on behalf of the receiving Party to the Regulatory Authorities in connection with any filing, application or request for Regulatory Approval in accordance with the terms of this Agreement; *provided* that reasonable measures shall be taken to assure confidential treatment of such Confidential Information to the extent practicable and consistent with Applicable Law;

10.3.3 made to its or its Affiliates' financial and legal advisors who have a need to know such disclosing Party's Confidential Information and are either under professional codes of conduct giving rise to expectations of confidentiality and non-use or under written agreements of confidentiality and non-use, in each case, substantially similar to the obligations of confidentiality and non-use of the receiving Party pursuant to this **Article 10** (Confidentiality and Non-Disclosure);

10.3.4 [***]

10.3.5 [***].

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10.3.6 For any disclosures made by the receiving Party pursuant to **Section 10.3.3**, **Section 10.3.4** and **Section 10.3.5**, such receiving Party shall remain responsible for any failure of the relevant Person to treat such Confidential Information as required under this **Article 10** (Confidentiality and Non-Disclosure). For clarity, in any case where the foregoing disclosure must be subject to obligations of confidentiality and non-use substantially similar to those under this **Article 10** (Confidentiality and Non-Disclosure), it is understood that the duration of such confidentiality and non-use obligations shall be no less than [***] from the date of disclosure.

10.4 Use of Name. Except as expressly provided in this Agreement, neither Party shall mention or otherwise use the name, logo or Trademark of the other Party or any of its Affiliates (or any abbreviation or adaptation thereof) in any publication, press release, marketing and promotional material, website or other form of publicity, without the prior written approval of such other Party. Notwithstanding the foregoing, the restrictions imposed by this **Section 10.4** shall not prohibit either Party from making any disclosure identifying the other Party that, in the opinion of the disclosing Party's counsel, is required by Applicable Law (including stock exchange rules); *provided* that such Party shall submit the proposed disclosure identifying the other Party in writing to the other Party as far in advance as reasonably practicable (and in no event less than [***] prior to the anticipated date of disclosure unless such proposed disclosure is required under Applicable Law, or the rules of an applicable securities exchange, in each case to be made in [***] or less) so as to provide a reasonable opportunity to comment thereon.

10.5 Public Announcements. Promptly following the Execution Date (and in any event within [***] thereafter), the Parties shall agree (such agreement not to be unreasonably withheld, conditioned or delayed) upon the content of a press release to be issued by each Party or by the Parties jointly to announce the collaboration and such press release(s) shall not otherwise be subject to the review procedures in this **Section 10.5**. Neither Party shall issue any other public announcement, press release or other public disclosure regarding this Agreement or the Parties' activities hereunder without the other Party's prior written consent (which shall not be unreasonably withheld, delayed or conditioned), except for any such disclosure regarding [***], or any other disclosure that is, in the opinion of the disclosing Party's counsel, required by Applicable Law or the rules of a stock exchange on which the securities of the disclosing Party are listed, or is otherwise expressly permitted in accordance with this **Article 10** (Confidentiality and Non-Disclosure). In the event a Party desires to make a public announcement regarding the payment of any milestone or that is, in the opinion of its counsel, required by Applicable Law or the rules of a stock exchange on which its securities are listed to make such a public disclosure, such Party shall submit the proposed disclosure in writing to the other Party as far in advance as reasonably practicable (and in no event less than [***] prior to the anticipated date of disclosure, unless such proposed disclosure is required under Applicable Law, or the rules of an applicable securities exchange, in each case to be made in [***] or less) so as to provide a reasonable opportunity to comment thereon.

10.6 Publications and Presentations.

10.6.1 [***].

10.6.2 [***].

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10.6.3 [***].

10.6.4 [***]:

(a) [***]

(b) [***]: (i) [***]; (ii) [***]; and (iii) [***]; *provided*, *however*, that [***].

10.7 Prior Confidentiality. Any Information disclosed by a Party or its Affiliate to the other Party or its Affiliate prior to the Execution Date under that certain Confidentiality Agreement between the Parties or their respective Affiliates dated March 14, 2017 shall be deemed to have been disclosed under this Agreement, and covered by the provisions of this **Article 10** (Confidentiality and Non-Disclosure).

10.8 Survival. All Confidential Information shall continue to be subject to the terms of this Agreement for the period set forth in **Section 10.1** (Confidentiality Obligations).

10.9 Residuals Disclaimer. Notwithstanding any other provision of this Agreement, the Parties agree that each Party will not be liable in any respect for the use of Confidential Information received by such Party hereunder (whether not such Confidential Information is deemed to be such Party's Confidential Information hereunder) by any of officers, directors, employees or agents of such Party or Affiliates of such Party, to the extent such Confidential Information is retained in the unaided memory of such officer, director, employee or agent.

ARTICLE 11
REPRESENTATIONS, WARRANTIES AND COVENANTS

11.1 Mutual Representations and Warranties. Denali and Sanofi each represents and warrants to the other, as of the Execution Date, as follows:

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11.1.1 Organization. It is duly organized, validly existing and in good standing under the laws of the jurisdiction of its organization, and has all requisite power and authority, corporate or otherwise, to execute, deliver and perform its obligations under this Agreement.

11.1.2 Authorization. The execution and delivery of this Agreement and the performance by it of its obligations hereunder have been duly authorized by all necessary corporate action, and do not violate (a) such Party's charter documents, bylaws or other organizational documents; (b) in any material respect, any agreement, instrument, or contractual obligation to which such Party is bound; (c) any requirement of any Applicable Law existing as of the Execution Date and applicable to such Party; or (d) any order, writ, judgment, injunction, decree, determination or award of any court or governmental agency in effect as of the Execution Date and applicable to such Party.

11.1.3 Binding Agreement. This Agreement is a legal, valid and binding obligation of such Party enforceable against it in accordance with its terms and conditions, subject to the effects of bankruptcy, insolvency or other laws of general application affecting the enforcement of creditor rights, judicial principles affecting the availability of specific performance and general principles of equity (whether enforceability is considered a proceeding at law or equity).

11.1.4 No Inconsistent Obligation. It is not under any obligation, contractual or otherwise, to any Person that conflicts with, or is inconsistent in any material respect with, the terms of this Agreement.

11.1.5 Debarment. Neither it nor any of its employees, nor to its knowledge, any of the agents performing hereunder, has ever been, is currently or is the subject of a proceeding that could lead to it or such employees or agents becoming, as applicable, a Debarred Entity or Debarred Individual, an Excluded Entity or Excluded Individual or a Convicted Entity or Convicted Individual. For purposes of this provision, the following definitions shall apply:

(a) A "**Debarred Individual**" is an individual who has been debarred by the FDA pursuant to 21 U.S.C. §335a (a) or (b) from providing services in any capacity to a Person who has an approved or pending drug or biological product application.

(b) A "**Debarred Entity**" is a corporation, partnership or association that has been debarred by the FDA pursuant to 21 U.S.C. §335a (a) or (b) from submitting or assisting in the submission of any abbreviated drug application, or a subsidiary or affiliate of a Debarred Entity.

(c) An "**Excluded Individual**" or "**Excluded Entity**" is (i) an individual or entity, as applicable, who has been excluded, debarred, suspended or is otherwise ineligible to participate in federal health care programs such as Medicare or Medicaid by the Office of the Inspector General (OIG/HHS) of the U.S. Department of Health and Human Services; or (ii) is an individual or entity, as applicable, who has been excluded, debarred, suspended or is otherwise ineligible to participate in federal procurement and non-procurement programs, including those produced by the U.S. General Services Administration (GSA).

(d) A "**Convicted Individual**" or "**Convicted Entity**" is an individual or entity, as applicable, who has been convicted of a criminal offense that falls within the ambit of 21 U.S.C. §335a (a) or 42 U.S.C. §1320a - 7(a), but has not yet been excluded, debarred, suspended or otherwise declared ineligible.

11.2 Additional Representations and Warranties of Denali. Denali further represents and warrants to Sanofi, as of the Execution Date [***], as follows:

11.2.1 No claim, judgment or settlement has been brought or obtained against Denali or any of its Affiliates relating to the Denali Patents or the Denali Know-How. No claim, litigation or administrative proceeding has been brought or, to Denali's knowledge, has been threatened in writing by any Person alleging, that (a) the Denali Patents are invalid or unenforceable; or (b) the Denali Patents, or the Denali Know-How, or the disclosing, copying, making, assigning or licensing of the Denali Patents or the Denali Know-How, or the Development or Commercialization of the Compounds or Products as contemplated herein, does or will violate, infringe, misappropriate or otherwise conflict or interfere with, any Patent or other intellectual property or proprietary right of any Person.

11.2.2 Neither Denali nor, to Denali's knowledge, any other owner of any of the Denali Patents has granted to any Third Party any rights under the Denali Patents to Exploit the Licensed Compounds or Licensed Products in any manner that conflicts with the rights therein granted to Sanofi under this Agreement. Denali has the right to grant the licenses and other rights granted to Sanofi under this Agreement and Denali has not granted any license, right, option or interest in, to or under the Denali Technology that is in conflict with the licenses granted to Sanofi under this Agreement.

11.2.3 (a) To Denali's knowledge, Denali has the right to Exploit all Denali Know-How and Denali Patents necessary to conduct the activities under the Programs with respect to Licensed Compounds and Licensed Products, and (b) the Development or Commercialization of the Licensed Compounds and Licensed Products as contemplated herein will not conflict with any other license or agreement to which Denali or any of its Affiliates is a party.

11.2.4 To Denali's knowledge and except as listed in **Schedule 11.2.4**: [***].

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11.2.5 **Schedule 6.5.1** contains a complete and accurate list of all Existing In-License Agreements. A complete and accurate copy of each contract between Denali and each such Person and all associated amendments, notices and waivers related to the performance of obligations thereunder was included in the electronic data room that it has made available to Sanofi ("**Data Room**"). Neither Denali nor, to Denali's knowledge, any counterparty is in breach of any Existing In-License Agreement. No party to any such agreement has threatened to terminate, nor alleged any breach under, any Existing In-License Agreement. Denali has not received any written notice from any counterparty to any of Existing In-License Agreements threatening to terminate such Existing In-License Agreement or alleging that Denali is in breach of any Existing In-License Agreement. Each Existing In-License Agreement is in full force and effect. None of the Denali Know-How disclosed to Sanofi contains any Information (as defined in the [***]) owned by any party to the [***] other than Denali or [***], and no such other Information, including [***] (each as defined in the [***]), has been disclosed to Denali or is necessary to conduct the activities contemplated by this Agreement.

11.2.6 **Schedule 1.40** contains a complete and correct list of Denali Patents for which Denali solely controls Prosecution and Maintenance ("**Denali Controlled Denali Patents**") and, to Denali's knowledge, a complete and correct list of Denali Patents for which Denali does not solely control Prosecution and Maintenance ("**Denali Licensed Patents**").

(a) The Denali Controlled Denali Patents have been filed, are being lawfully Prosecuted and all applicable fees have been paid on or before the due date for payment. The Denali Controlled Denali Patents are being prosecuted in the respective patent offices in the Territory in accordance with Applicable Law. To Denali's knowledge, the Denali Controlled Denali Patents that have issued as of the Execution Date are valid. Denali has not intentionally taken or failed to take any action that would cause the Denali Controlled Denali Patents that have issued as of the Execution Date to be unenforceable. Denali is the sole owner of all Denali Controlled Denali Patents.

(b) To Denali's knowledge, the Denali Licensed Patents are being prosecuted in the respective patent offices in the Territory in accordance with Applicable Law. To Denali's knowledge, the Denali Licensed Patents have been filed, are being lawfully Prosecuted and all applicable fees have been paid on or before the due date for payment. To Denali's knowledge, the Denali Licensed Patents that have issued are valid and enforceable.

11.2.7 To Denali's knowledge, no Person is infringing or threatening to infringe or misappropriating or threatening to misappropriate the Denali Patents or the Denali Know-How.

11.2.8 No written claim has been filed, or to Denali's knowledge, threatened in writing, against it by any Third Party alleging that the conception, development or reduction to practice of any of the Denali Patents or Denali Know-How constitute or involve the misappropriation of trade secrets or other violation of the rights or property of any Person.

11.2.9 Denali has conducted, and to Denali's knowledge, its contractors and consultants have conducted, all Development of the Licensed Compounds in accordance with Applicable Law.

11.2.10 **Schedule 4.1** contains a complete and accurate list of all of Denali's Third Party Providers of manufacturing services and technology performing activities with respect to the Licensed Compounds or Licensed Products as of the Execution Date. A complete and accurate copy of each contract between Denali and each such Third Party Provider and all associated amendments and waivers pertaining to the performance of obligations thereunder was included in the Data Room. Neither Denali nor, to Denali's knowledge, any counterparty is in material breach of any such agreement. No party thereto has threatened to terminate, nor alleged any material breach under, any such agreement. Denali has not received any written notice from any counterparty to any such agreement threatening to terminate such agreement or alleging that Denali is in breach of any such agreement. Each such agreement is in full force and effect.

11.2.11 **Schedule 11.2.11** sets forth [***], in each case of the Execution Date.

11.2.12 The inventions claimed or covered by the Denali Controlled Denali Patents (i) were not conceived, discovered, developed or otherwise made in connection with any research activities funded, in whole or in part, by the federal government of the United States or any agency thereof; (ii) are not a "subject invention" as that term is described in 35 U.S.C. §201(e); (iii) are not otherwise subject to the provisions of the Patent and Trademark Law Amendments Act of 1980, as amended, codified at 35 U.S.C. §§200-212, as amended, or any regulations promulgated pursuant thereto, including in 37 C.F.R. Part 401; and (iv) are not the subject of any licenses, options or other rights of any Governmental Authority, within or outside the United States. In the event that any inventions Covered or claimed by the Denali Controlled Denali Patents have been conceived, discovered, developed or otherwise made in connection with any research and development activities funded, in whole or in part, by the federal government of the United States or any agency thereof, Denali has complied with the provisions of the Patent and Trademark Law Amendments Act of 1980, as amended, codified at 35 U.S.C. §§200-212, as amended, as well as any regulations promulgated pursuant thereto, including in 37 C.F.R. Part 401.

11.2.13 All current and former officers, employees, agents and consultants of Denali or any of its Affiliates who are inventors of or have otherwise contributed in a material manner to the creation or development of any Denali Controlled Denali Patents have executed and delivered to Denali or such Affiliate an assignment or other agreement regarding the protection of proprietary information and the assignment to Denali or such Affiliate of any Denali Controlled Denali Patents.

11.3 Additional Covenants of Denali. Denali covenants to Sanofi as follows:

11.3.1 Denali shall [***].

11.3.2 Denali shall (a) [***]; (b) [***]; (c) [***]; and (d) [***]. Denali shall [***].

11.3.3 Denali shall [***].

11.3.4 If, during the Term, [***], Denali shall [***].

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11.4 Additional Representations and Warranties of Sanofi. Sanofi further represents and warrants to Denali, as of the Execution Date [***], as follows:

11.4.1 [***].

11.4.2 [***].

11.4.3 [***].

11.4.4 [***].

11.4.5 [***].

11.4.6 [***].

11.4.7 [***].

11.4.8 **Schedule 11.4.8** sets forth [***].

11.5 Additional Covenants of Sanofi. Sanofi covenants to Denali as follows:

11.5.1 Sanofi shall [***].

11.5.2 Sanofi shall (a) [***], (b) [***], and (c) [***].

11.5.3 Neither Sanofi nor any of its Affiliates will [***].

11.5.4 If, during the Term, [***], Sanofi shall [***].

11.6 DISCLAIMER. EXCEPT FOR THE EXPRESS REPRESENTATIONS AND WARRANTIES SET FORTH IN **SECTION 11.1** (MUTUAL REPRESENTATIONS AND WARRANTIES), **SECTION 11.2** (ADDITIONAL REPRESENTATIONS AND WARRANTIES OF DENALI), **SECTION 11.4** (ADDITIONAL REPRESENTATIONS AND WARRANTIES OF SANOFI) , NEITHER PARTY MAKES ANY REPRESENTATIONS OR GRANTS ANY WARRANTIES, EXPRESS OR IMPLIED, EITHER IN FACT OR BY OPERATION OF LAW, BY STATUTE OR OTHERWISE, AND EACH PARTY SPECIFICALLY DISCLAIMS ANY OTHER WARRANTIES, WHETHER WRITTEN OR ORAL, OR EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OF QUALITY, MERCHANTABILITY OR FITNESS FOR A PARTICULAR USE OR PURPOSE OR ANY WARRANTY AS TO THE VALIDITY OF ANY PATENTS OR THE NON-INFRINGEMENT OF ANY INTELLECTUAL PROPERTY RIGHTS OF THIRD PARTIES.

ARTICLE 12
INDEMNITY; LIMITATIONS OF LIABILITY; INSURANCE

12.1 Indemnification of Denali. Sanofi shall indemnify Denali, its Affiliates and its and their respective directors, officers, employees, and agents ("**Denali Indemnitees**") and defend and hold each of them harmless, from and against any and all losses, damages, liabilities, penalties, costs and expenses (including reasonable attorneys' fees and expenses) (collectively,

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"**Indemnified Losses**") in connection with any and all suits, investigations, claims or demands of Third Parties (collectively, "**Third Party Claims**") incurred by or rendered against the Denali Indemnitees arising from or occurring as a result of:

(a) the Development, Manufacture, Commercialization or other Exploitation of Compounds or Products by or under the authority of Sanofi (other than by Denali, its Affiliates or Sublicensees) either during the Term or after the termination of this Agreement (with respect to a Terminated Product), including any Additional CNS Development Activities conducted by or under the authority of Sanofi, but in each case excluding any of the foregoing associated with any Cost Profit Sharing Product in a Cost Profit Sharing Country;

(b) the negligence, reckless conduct or willful misconduct on the part of Sanofi or its Affiliates or their respective directors, officers, employees, and agents in performing its or their obligations under this Agreement; or

(c) a breach by Sanofi of this Agreement, including any breach of a representation, warranty or covenant by Sanofi made under **Article 11** (Representations, Warranties and Covenants);

except in the case of clauses (a) through (c), for those Indemnified Losses for which Denali, in whole or in part, has an obligation to indemnify Sanofi pursuant to **Section 12.2** (Indemnification of Sanofi), as to which Indemnified Losses each Party shall indemnify the other to the extent of their respective liability for such Indemnified Losses.

12.2 Indemnification of Sanofi. Denali shall indemnify Sanofi, its Affiliates and its and their respective directors, officers, employees and agents ("**Sanofi Indemnitees**"), and defend and hold each of them harmless, from and against any and all Indemnified Losses in connection with any and all Third Party Claims incurred by or rendered against the Sanofi Indemnitees arising from or occurring as a result of:

(a) the Development, Manufacture, Commercialization or other Exploitation of the CNS Compounds and CNS Products, by or under the authority of Denali (other than by Sanofi, its Affiliates or Sublicensees) either during the Term or after the termination of this Agreement (with respect to a Terminated Product), including any Additional CNS Development Activities conducted by or under the authority of Denali, but in each case excluding any of the foregoing associated with Cost Profit Sharing Product in a Cost Profit Sharing Country;

(b) the negligence, reckless conduct or willful misconduct on the part of Denali or its Affiliates or its or their respective directors, officers, employees, and agents in performing its obligations under this Agreement;

(c) a breach by Denali of this Agreement, including any breach of a representation, warranty or covenant by Denali made under Article 11 (Representations, Warranties and Covenants).

except, in the case of clause (a) through (c) above for those Indemnified Losses for which Sanofi, in whole or in part, has an obligation to indemnify Denali pursuant to **Section 12.1** (Indemnification of Denali), as to which Indemnified Losses each Party shall indemnify the other to the extent of their respective liability for the Indemnified Losses.

12.3 Certain Indemnified Losses. Any Indemnified Losses and all Out-of-Pocket Costs incurred by a Party to conduct its indemnification obligations under **Section 12.1** (Indemnification of Denali) or **Section 12.2** (Indemnification of Sanofi), (other than those Indemnified Losses and Out-of-Pocket Costs that result from the [***]), in connection with any Third Party Claim brought against either Party resulting directly or indirectly from (a) [***] or (b) [***]. If either Party learns of any Third Party Claim with respect to Indemnified Losses covered by this **Section 12.3**, such Party shall provide the other Party with prompt written notice thereof. The Parties shall confer with respect to how to respond to such Third Party Claim and how to handle such Third Party Claim in an efficient manner. In the absence of such an agreement, each Party shall have the right to take such action as it deems appropriate.

12.4 Notice of Claim. All indemnification claims in respect of a Party, its Affiliates or their respective directors, officers, employees and agents shall be made solely by such Party to this Agreement ("**Indemnified Party**"). Subject to **Section 12.3** (Certain Indemnified Losses), the Indemnified Party shall give the indemnifying Party prompt written notice ("**Indemnification Claim Notice**") of any Indemnified Losses or discovery of fact upon which such Indemnified Party intends to base a request for indemnification under this **Article 12** (Indemnity; Limitations of Liability; Insurance), but in no event shall the indemnifying Party be liable for any Indemnified Losses to the extent such Indemnified Losses arise from any delay in providing such notice. Each Indemnification Claim Notice must contain a description of the claim and the nature and amount of such Indemnified Loss (to the extent that the nature and amount of such Indemnified Loss is known at such time). The Indemnified Party shall furnish promptly to the indemnifying Party copies of all papers and official documents received in respect of any Indemnified Losses and Third Party Claims.

12.5 Control of Defense.

12.5.1 In General. Subject to the provisions of **Section 8.4** (Infringement Claims by Third Parties), **Section 8.5** (Invalidity or Unenforceability Defenses or Actions) and **Section 8.6.3** (Third Party Claims) and of **Section 12.3** (Certain Indemnified Losses), at its option, the indemnifying Party may assume the defense of any Third Party Claim by giving written notice to the Indemnified Party within [***] after the indemnifying Party's receipt of an Indemnification Claim Notice. The assumption of the defense of a Third Party Claim by the indemnifying Party shall not be construed as an acknowledgment that the indemnifying Party is liable to indemnify the Indemnified Party in respect of the Third Party Claim, nor shall it constitute a waiver by the indemnifying Party of any defenses it may assert against the Indemnified Party's claim for indemnification. Upon assuming the defense of a Third Party Claim pursuant to this **Section 12.5.1**, the indemnifying Party may appoint as lead counsel in the defense of the Third Party Claim any legal counsel selected by the indemnifying Party which

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shall be reasonably acceptable to the Indemnified Party. In the event the indemnifying Party assumes the defense of such a Third Party Claim, the Indemnified Party shall immediately deliver to the indemnifying Party all original notices and documents (including court papers) received by the Indemnified Party in connection with such Third Party Claim. Should the indemnifying Party assume the defense of such a Third Party Claim, except as provided in **Section 12.5.2** (Right to Participate in Defense), the indemnifying Party shall not be liable to the Indemnified Party for any legal expenses subsequently incurred by such Indemnified Party in connection with the analysis, defense or settlement of the Third Party Claim unless specifically requested in writing by the indemnifying Party. In the event that it is ultimately determined that the indemnifying Party is not obligated to indemnify, defend or hold harmless the Indemnified Party from and against such Third Party Claim, the Indemnified Party shall reimburse the indemnifying Party for any Indemnified Losses incurred by the indemnifying Party in its defense of such Third Party Claim.

12.5.2 Right to Participate in Defense. Without limiting **Section 12.5.1** (In General), any Indemnified Party shall be entitled to participate in, but not control, the defense of such Third Party Claim and to employ counsel of its choice for such purpose; *provided* that such employment shall be at the Indemnified Party's own expense unless (a) the employment thereof, and the assumption by the indemnifying Party of such expense, has been specifically authorized by the indemnifying Party in writing; (b) the indemnifying Party has failed to assume the defense and employ counsel in accordance with **Section 12.5.1** (In General) (in which case the Indemnified Party shall control the defense); or (c) the interests of the Indemnified Party and the indemnifying Party with respect to such Third Party Claim are sufficiently adverse to prohibit the representation by the same counsel of both Parties under Applicable Law, ethical rules or equitable principles.

12.5.3 Settlement. With respect to any Indemnified Losses relating solely to the payment of money damages in connection with a Third Party Claim and that shall not result in the Indemnified Party's becoming subject to injunctive relief, specific performance or otherwise adversely affect the business of the Indemnified Party in any manner, and as to which the indemnifying Party shall have acknowledged in writing the obligation to indemnify the Indemnified Party hereunder, the indemnifying Party shall have the sole right to consent to the entry of any judgment, enter into any settlement or otherwise dispose of such Indemnified Loss, on such terms as the indemnifying Party, in its sole discretion, shall deem appropriate. With respect to all other Indemnified Losses in connection with Third Party Claims, where the indemnifying Party has assumed the defense of the Third Party Claim in accordance with **Section 12.5.1** (In General), the indemnifying Party shall have authority to consent to the entry of any judgment, enter into any settlement or otherwise dispose of such Indemnified Loss; *provided* that it obtains the prior written consent of the Indemnified Party (which consent shall not be unreasonably withheld, delayed or conditioned). If the indemnifying Party does not assume and conduct the defense of a Third Party Claim as provided above, the Indemnified Party may defend against such Third Party Claim. Regardless of whether the indemnifying Party chooses to defend or prosecute any Third Party Claim, no Indemnified Party shall admit any liability with respect to, or settle, compromise or dispose of, any Third Party Claim in a manner that would have a material adverse effect on the Indemnified Party or admit wrongdoing on behalf of the Indemnified Party, without the prior written consent of the indemnifying Party. The indemnifying Party shall not be liable for any settlement, compromise or other disposition of

an Indemnified Loss by an Indemnified Party that is reached without the written consent of the indemnifying Party.

12.5.4 Cooperation. Regardless of whether the indemnifying Party chooses to defend or prosecute any Third Party Claim, the Indemnified Party shall, and shall cause each indemnitee to, cooperate in the defense or prosecution thereof and shall furnish such records, information and testimony, provide such witnesses and attend such conferences, discovery proceedings, hearings, trials and appeals as may be reasonably requested in connection therewith. Such cooperation shall include access during normal business hours afforded to the indemnifying Party to, and reasonable retention by the Indemnified Party of, records and information that are reasonably relevant to such Third Party Claim, and making Indemnified Parties and other employees and agents available on a mutually convenient basis to provide additional information and explanation of any material provided hereunder, and the indemnifying Party shall reimburse the Indemnified Party for all its reasonable out-of-pocket expenses in connection therewith.

12.5.5 Expenses. Except as provided above, the reasonable and verifiable costs and expenses, including fees and disbursements of counsel, incurred by the Indemnified Party in connection with any Third Party Claim shall be reimbursed on a Calendar Quarter basis in arrears by the indemnifying Party, without prejudice to the indemnifying Party's right to contest the Indemnified Party's right to indemnification and subject to refund in the event the indemnifying Party is ultimately held not to be obligated to indemnify the Indemnified Party.

12.6 Special, Indirect, and Other Losses. EXCEPT (A) [***], (B) [***], AND (C) [***], NEITHER PARTY NOR ANY OF ITS AFFILIATES SHALL BE LIABLE FOR INDIRECT, INCIDENTAL, SPECIAL, EXEMPLARY, PUNITIVE OR CONSEQUENTIAL DAMAGES, INCLUDING LOSS OF PROFITS OR BUSINESS INTERRUPTION (TO THE EXTENT THE SAME ARE CONSEQUENTIAL DAMAGES), HOWEVER CAUSED AND ON ANY THEORY OF LIABILITY, WHETHER IN CONTRACT, TORT, NEGLIGENCE, BREACH OF STATUTORY DUTY OR OTHERWISE IN CONNECTION WITH, OR ARISING IN ANY WAY OUT OF, THE TERMS OF THIS AGREEMENT OR THE TRANSACTIONS CONTEMPLATED HEREBY OR THE USE OF A COMPOUND OR PRODUCT, EVEN IF ADVISED OF THE POSSIBILITY OF SUCH DAMAGE.

12.7 Insurance. Each Party will procure and maintain liability insurance with carriers rated "A-" AM Best rating or equivalent, including product liability insurance, with minimum limits of [***] per claim and in the aggregate, with respect to its activities hereunder and which are consistent with normal business practices of prudent companies similarly situated at all times during which any Product is being commercially distributed or sold. It is understood that such insurance will not be construed to create a limit of either Party's liability with respect to its indemnification obligations under this **Article 12** (Indemnity; Limitations of Liability; Insurance). Clinical trials insurance must be implemented by the sponsor of the clinical trial in compliance with local Applicable Laws. Each Party will provide the other with written evidence of such insurance upon request. Product liability policies will be maintained for [***] following termination of this Agreement. Notwithstanding the foregoing, (a) Sanofi may self-insure, in whole or in part, the

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insurance requirements described above; and (b) Denali may self-insure, in whole or in part, the insurance requirements described [***]).

ARTICLE 13
TERM AND TERMINATION

13.1 Term. This Agreement shall commence on the Execution Date (subject to **Section 14.1** (HSR Act Compliance)) and, unless earlier terminated as set forth below, shall continue in force and effect until the expiration of Sanofi's payment obligations under this Agreement (such period, the "**Term**").

13.2 Termination for Material Breach. If either Party ("**Non-Breaching Party**") believes that the other Party ("**Breaching Party**") has materially breached this Agreement, then the Non-Breaching Party may deliver notice of such material breach to the Breaching Party ("**Default Notice**"). If the Breaching Party does not dispute that it has committed a material breach of this Agreement and the Breaching Party fails to cure such breach within [***] after receipt of the Default Notice, the Non-Breaching Party may terminate this Agreement upon written notice to the Breaching Party; *provided* that if such material breach is with respect to only a Program (and not with respect to this Agreement in its entirety), such termination shall be limited to such Program. If the Breaching Party disputes the Default Notice within [***] cure period, the dispute shall be resolved pursuant to **Section 15.6.3** (ADR). If, as a result of the application of such dispute resolution procedures, the Breaching Party is determined to have materially breached this Agreement ("**Adverse Ruling**") and the Breaching Party fails to complete the actions specified by the Adverse Ruling to cure such material breach within any of the remaining [***] cure period after such ruling is issued, then the Non-Breaching Party may terminate this Agreement upon written notice to the Breaching Party; [***].

13.3 For Convenience. Sanofi may terminate this Agreement for any or no reason, upon [***] prior written notice to Denali: (a) in its entirety; (b) with respect to a particular Program; or (c) on a Program-by-Program basis, with respect to any of the following regions, which taken together comprise the entire world: (i) the continents of Europe and Africa; (ii) the continents of North America and South America; or (iii) the continents of Asia, Australia and Antarctica and those countries in Oceania other than Australia. For purposes of this **Section 13.3**, each of the regions described in clause (i), (ii) and (iii) shall consist of the countries listed on **Schedule 13.3** attached to this Agreement. For the avoidance of doubt, if Sanofi exercises its right to terminate this Agreement under this **Section 13.3** with respect to one or more regions described in clause (c) above, such right shall apply to the entire region described in sub-clause (i), (ii) or (iii), as the case may be, and not to individual countries or continents within any such region, and such terminated region(s) (or the whole Territory, if this Agreement is terminated in its entirety under this **Section 13.3**) with respect to the terminated Program shall be referred to as the "**Terminated Area**".

13.4 Termination for Insolvency. Either Party may terminate this Agreement in its entirety at any time during the Term by giving written notice to the other Party if the other Party files in any court or agency pursuant to any statute or regulation of any state or country a petition in bankruptcy or insolvency or for reorganization or for an arrangement or for the appointment of a receiver or trustee for the other Party or its assets, or if the other Party is served with an involuntary

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petition against it, filed in any insolvency proceeding, and such petition shall not be dismissed with [***] after the filing thereof, or if the other Party makes a general assignment for the benefit of creditors.

13.5 [***]. [***].

13.6 Termination for Safety. Sanofi will have the right to terminate this Agreement with respect to an affected Program or Product (and any other Product containing the same Compound), upon [***] prior written notice to Denali, if a Material Safety Event occurs or is identified by a Regulatory Authority [***]. In addition, subject to this **Section 13.6**, Sanofi will have the right to terminate this Agreement with respect to an affected Program or Product (and any other Product containing the same Compound), upon [***] prior written notice to Denali, if as a result of a Material Safety Event, [***]. Any notice of termination issued by Sanofi to Denali under this **Section 13.6** (Termination for Safety) shall include a summary of any Material Safety Event(s) [***]. During the applicable notice period, each Party will continue to perform all of its obligations under this Agreement then in effect and, to the extent applicable, bear their respective shares of all Development Costs and Allowable Expenses incurred during such notice period.

13.7 Termination for Non-Compliance of HSR Condition. Either Party will have the right to terminate this Agreement in its entirety as provided in **Section 14.1** (HSR Act Compliance).

13.8 Effects of Termination. In the event of any termination of this Agreement in its entirety or with respect to a Program or Product(s) (each such terminated Program or Product(s) (including all Compounds included in such terminated Product(s)) or, if this Agreement is terminated in its entirety, all Programs, Compounds and Products, "**Terminated Portion**") or Terminated Area, subject to **Section 13.10** (Accrued Rights; Surviving Obligations), the following shall apply:

13.8.1 Effects of Termination by Sanofi for Convenience or Safety or by Denali for Cause on Terminated Denali Products. Upon any termination by Sanofi pursuant to **Section 13.3** (For Convenience) or **Section 13.6** (Termination for Safety) or termination by Denali pursuant to **Section 13.2** (Termination for Material Breach), **Section 13.4** (Termination for Insolvency) [***], the following will apply solely with respect to (x) Licensed Compounds and Licensed Products, and (y) [***] (such compounds and products, "**Terminated Denali Products**"):

(a) **Licenses**. All rights and licenses granted by Denali under **Article 6** (License Grants; Exclusivity), except to the extent any Terminated Denali Products are the subject of a Fully Paid-Up License in any country of the Terminated Area pursuant to **Section 7.5.3(a)** (Duration of Accruals; Paid-Up), and all obligations of Sanofi with respect thereto, shall immediately terminate with respect to the Terminated Denali Products; all rights and licenses granted by Sanofi under **Article 6** (License Grants; Exclusivity), and all obligations of Denali with respect thereto, shall immediately terminate with respect to the Terminated Denali Products;

(b) **Patent Rights.** [***];

(c) **New Licenses**. Sanofi shall, and hereby does effective as of the effective date of termination, grant Denali (A) an exclusive, irrevocable license in the Terminated

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Area, with the right to grant multiple tiers of sublicenses, under Sanofi Know-How and Sanofi's interest in any Joint Program Know-How, in each case, [***] ("**Sanofi Unblocking Know-How**"); and (B) an exclusive, irrevocable license in the Terminated Area, with the right to grant multiple tiers of sublicenses, under Sanofi Patents and Sanofi's interest in any Joint Program Patent claiming or covering any Sanofi Unblocking Know-How [***] (collectively, the "**Sanofi Unblocking Patent Rights**"), in each case [***]. For clarity, the scope of the Sanofi Unblocking Know-How and Sanofi Unblocking Patent Rights subject to the foregoing license shall be determined based on [***], regardless of whether [***]. Further such license [***], except to the extent provided in **Section 13.8.1(c)(ii)** and [***]:

(i) [***].

(ii) [***].

(iii) [***].

(iv) [***], and [***].

(d) **Regulatory Materials and Trademarks.** Sanofi shall assign to Denali (or its designee) all Regulatory Approvals, Regulatory Documentation and Product Trademarks Controlled by Sanofi or its Affiliates for the Terminated Denali Products and in the Terminated Area, in each case, unless otherwise required by Applicable Law or requested by Denali, the foregoing assignment (or availability) shall be made within [***] after the effective date of such termination of this Agreement, and if such assignment cannot be made under Applicable Law within such period, as soon as practicable thereafter. [***]. Sanofi shall provide the applicable Regulatory Authority a letter confirming this Right of Reference at any time within [***] after Denali's request and shall take such other actions and execute such other documents as Denali may reasonably request to further confirm and give effect to this Right of Reference. Notwithstanding the definition of Confidential Information, all such Regulatory Documentation and Regulatory Approvals in the Terminated Area for the Terminated Denali Products and all Joint Program Know-How that is solely specific to the Terminated Denali Products shall be deemed to be the Confidential Information of Denali, and not Sanofi, following Sanofi's assignment of such Regulatory Documentation and Regulatory Approvals to Denali pursuant to this **Section 13.8.1(d)**.

(e) **Technology Transfer.** Sanofi shall provide to Denali the Sanofi Unblocking Know-How (to the extent licensed under **Section 13.8.1(c)** (New Licenses)), Regulatory Documentation, Clinical Data and other Information pertaining to the Terminated Denali Products in the Terminated Area (to the extent such items exist as of the date of such termination), and Denali shall have the right to use and disclose the same in connection with the Exploitation of the Terminated Denali Products. Sanofi shall have no obligation to translate any such Sanofi Know-How, Regulatory Documentation, Clinical Data or other Information into English or any other language.

(f) **Transition Assistance**. The following shall also apply:

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(i) **Development**. In the event Sanofi is conducting (or is having conducted on its behalf) any (a) on-going Clinical Studies or non-clinical studies pertaining to any Terminated Denali Product in the Terminated Area, or (b) any manufacturing process development activities (including formulation studies, stability studies, scale up tests, etc.) solely related to any such Terminated Denali Product, in each case following the effective date of such termination, Sanofi agrees, at Denali's request, (A) [***], to continue to conduct or transition to Denali (or its designee(s)) the conduct of such studies or activities within [***] ("**Denali Development Wind-Down Period**") after the effective date of such termination (to the extent permitted by Applicable Law [***]; or (B) to terminate such Clinical Studies, non-clinical studies, manufacturing process development or portions thereof [***]. Notwithstanding the foregoing, Denali shall [***].

(ii) **Commercialization**. If this Agreement is terminated after the First Commercial Sale of a Terminated Denali Product in the Terminated Area, Sanofi, its Affiliates and its Sublicensees shall continue to fulfill orders for the Terminated Area through their respective then-existing distribution network of internal and external distributors of such Terminated Denali Product, in accordance with the terms and conditions of this Agreement, in each country for which Regulatory Approval therefor has been obtained, for [***] after the effective date of termination ("**Commercialization Wind-down Period**"); [***]; *provided, further*, that Sanofi, its Affiliates and its Sublicensees shall cease any such activities being conducted pursuant to this **Section (f)(ii)**, or any portion thereof, in a given country within the Terminated Area upon [***] notice by Denali requesting that such activities (or portion thereof) be ceased. Notwithstanding any other provision of this Agreement, during the Commercialization Wind-down Period, Sanofi's and its Affiliates' and Sublicensees' rights with respect to applicable Terminated Denali Product(s) in the Terminated Area shall be non-exclusive and, without limiting the foregoing, Denali shall have the right to engage one or more other distributor(s) or licensee(s) of such Terminated Denali Product(s) in any country within the Terminated Area. Any Terminated Denali Product sold or disposed of by Sanofi, its Affiliates or its Sublicensees in any country within the Terminated Area during the Commercialization Wind-down Period shall be subject to applicable payment obligations under **Article 7** (Payments). In addition, if at the effective time of such termination, Sanofi or its Affiliates are undertaking Detailing or MSL Activities with respect to a particular Terminated Denali Product in any country within the Terminated Area, then, at Denali's request, the Parties will negotiate and agree upon a plan for the orderly wind down of such activities for a period not to exceed [***]. Any FTE Costs or Out-of-Pocket Costs incurred by Sanofi or its Affiliates in accordance with such plan for the wind down of Sanofi's activities shall be (a) reimbursed by Denali if the relevant Terminated Denali Product is not, immediately prior to the effective date of such termination, a Cost Profit Sharing Product; or (b) continue to be allocated towards Allowable Expenses until such wind down is complete, if the relevant Terminated Denali Product is a Cost Profit Sharing Product immediately prior to the effective date of such termination.

(iii) **Supply**.

(A) Except to the extent required for Sanofi to fulfill its obligations pursuant to **Section 13.8.1(f)(i)** (Development) and **Section 13.8.1(f)(ii)** (Commercialization), (x) Denali will have the right to purchase from Sanofi any non-expired

inventory of materials used to Manufacture the Terminated Denali Product(s), and bulk or finished form of the Terminated Denali Product that exists as of the effective date of termination of this Agreement at [***] with respect thereto (to the extent any portion of such Manufacturing Costs were not previously shared by Denali). [***]. Denali will notify Sanofi as soon as practicable and in no event later than [***] after the date of termination whether Denali elects to exercise the rights set forth in this **Section 13.8.1 (f) (iii)(A)**.

(B) Upon Denali's request, (a) Sanofi shall either assign to Denali Sanofi's agreement(s) with its Third Party Provider for the Terminated Denali Products for the Terminated Area and placebo thereof, to the extent such agreements are assignable under the terms thereof or Applicable Law, or alternatively, use reasonable efforts to facilitate Denali's entering into a direct supply agreement with such Third Party Provider of such Terminated Denali Products and placebo thereof on comparable terms to those between Sanofi and such Third Party Provider (in each case assuming Sanofi is then obtaining supply of Terminated Denali Products or placebo from a Third Party Provider), *provided, however*, that Sanofi will not be obligated to pay any consideration in order to effectuate any such agreement between Denali and Third Party; and (b) except in the case of termination of this Agreement by Sanofi pursuant to **Section 13.6** (Termination for Safety) and in such case, solely with respect to the Terminated Denali Product(s) that caused such termination, [***]. If so requested by either Party, the Parties will negotiate and enter into a supply agreement on reasonable and customary terms under which Sanofi will supply Denali with such Terminated Denali Products for the Terminated Area, but the execution of such agreement shall not limit or be a condition to Sanofi performing its obligations under this **Section 13.8.1(f)(iii)(B)**.

(g) For clarity, Denali agrees to indemnify the Sanofi Indemnitees and defend and hold each of them harmless, from and against any and all Indemnified Losses in connection with any and all Third Party Claims incurred or rendered against the Sanofi Indemnitees arising from or occurring as a result of the Development, Manufacture, Commercialization or other Exploitation of any Terminated Denali Product in the Terminated Area in accordance with **Section 12.2** (Indemnification of Sanofi) after the effective date of termination, and any such termination by Denali shall not limit Denali's obligation to indemnify Sanofi for any such Third Party Claims made by such Third Party related to the Exploitation of any Terminated Denali Product after the effective date of termination.

(h) **Cooperation**. Without limiting the foregoing, each Party shall use Commercially Reasonable Efforts to cooperate with the other Party to effect a smooth and orderly transition in the Terminated Portions in the Terminated Area in a prompt and expeditious manner in accordance with the terms of this Agreement. If Sanofi has entered into contracts that solely pertain to one or more Terminated Denali Product(s) in the Terminated Area with Third Parties (other than contract manufacturers described in **Section 13.8.1(f)** (Transition Assistance)) whose services are reasonably necessary for Denali to assume responsibility for the Terminated Denali Product(s) in the Terminated Area and corresponding activities, then Sanofi shall, to the extent reasonably possible and requested in writing by Denali, assign all of such Third Party contracts to Denali.

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(i) **Other Matters if Termination is Under Section 13.3 is Limited to a Particular Region**. To the extent the applicable termination is by Sanofi pursuant to **Section 13.3** (For Convenience) and the Terminated Area is one or more regions, the following shall also apply:

(i) With respect to the applicable Terminated Portion, each country of the Terminated Area shall cease to be a country within the Territory and the definition of "Territory" in **Section 1.147** ("Territory" definition) shall be deemed to be amended accordingly and all references to a Major Market shall be deemed to be references to a "Major Market within the Territory";

(ii) Notwithstanding any other provision of this Agreement, including **Section 1.39** ("Denali Know-How" definition), **Section 3.3.2** (Cooperation), **Section 3.4.4** (Regulatory Data) and **Section 6.1** (License Grants to Sanofi), except with respect to safety data required be shared in accordance with the Pharmacovigilance Agreement between the Parties, Denali shall not have any obligation to make available to Sanofi any Information with respect to a Terminated Denali Product generated by or on behalf of Denali, its Affiliates or licensees for the countries within the Terminated Area following any such termination and Sanofi shall have no rights to, and the licenses and rights granted by Denali to Sanofi under this Agreement shall not include, any such Information;

(iii) Upon notice by one Party to the other Party, the Parties shall promptly meet and agree on appropriate downward adjustments (as further described below) to (x) [***]; (y) [***]; and (z) [***]. In each case, such adjustment shall be [***]; *provided* that [***].

13.8.2 Effects of Termination by Sanofi for Cause on Terminated Denali Products. Upon any Termination by Sanofi pursuant to **Section 13.2** (Termination for Material Breach), **Section 13.4** (Termination for Insolvency), [***], the following will apply solely with respect to Terminated Denali Products:

(a) **Licenses**. All rights and licenses granted by Denali under **Article 6** (License Grants; Exclusivity), except to the extent any Terminated Denali Products are subject of a Fully Paid-Up License in any country of the Terminated Area pursuant to **Section 7.5.3(a)** (Duration of Accruals; Paid-Up), and all obligations of Sanofi with respect thereto, shall immediately terminate with respect to the Terminated Denali Products; all rights and licenses granted by Sanofi under **Article 6** (License Grants; Exclusivity), and all obligations of Denali with respect thereto, shall immediately terminate with respect to the Terminated Denali Products.

(b) **Regulatory Materials and Trademarks**. Sanofi shall assign to Denali (or its designee) all Regulatory Approvals and the INDs in the Terminated Area for each of the Terminated Denali Product(s) then being Developed or Commercialized, and will transfer to Denali all Regulatory Documentation in the countries within the Terminated Area relating to such Terminated Denali Products (subject to any redactions of such Regulatory Documentation relating to solely to products controlled by Sanofi that are not the Terminated Denali Products). Sanofi shall assign to Denali (or its designee) all Product Trademarks for the Terminated Denali Products

Controlled by Sanofi or its Affiliates in the countries within the Terminated Area. In each case, unless otherwise required by Applicable Law or requested by Denali, the foregoing assignment shall be made within [***] after the effective date of such a termination of this Agreement, and if such assignment cannot be made under Applicable Law within such period, as soon as practicable thereafter. [***]. Notwithstanding the definition of Confidential Information, each Regulatory Approval or, if no Regulatory Approval exists, the application for Regulatory Approval, Regulatory Documentation or IND for any Terminated Denali Products in the Terminated Area and all Joint Program Know-How that is solely specific to a Terminated Denali Product(s) shall be deemed to be the Confidential Information of Denali and not Sanofi, following Sanofi's assignment of such Regulatory Documentation and Regulatory Approvals to Denali pursuant to this **Section 13.8.2(b)**.

(c) **Inventory**. Sanofi will have [***] after the date of such a termination to sell off any remaining inventories and complete the Manufacture and sale of any work-in-progress, after which Denali will be obligated to purchase from Sanofi any of the remaining non-expired inventory of materials used to Manufacture any Terminated Denali Product(s), and bulk or finished form of any Terminated Denali Product(s), that existed as of the effective date of termination of this Agreement and was intended for use or sale in the Terminated Area at [***] with respect thereto (to the extent any portion of such Manufacturing Costs were not previously shared by Denali). In addition, Denali will be obligated to purchase any work-in-progress intended for use in the Terminated Area at [***], or by mutual agreement with respect to such work-in-progress.

(d) **Transition Assistance.** With respect to the post-termination wind down and transfer to Denali of Clinical Studies, Manufacturing or Commercialization activities being conducted by or under the authority of Sanofi in the Terminated Area as of the date of termination, Sanofi will provide (or cause to be provided) reasonable transition assistance to Denali (or its designee(s)), at the applicable FTE Rate for Sanofi's services in connection with such transition, for a period of no more than [***] after the effective date of such a termination (unless such period is extended by the agreement of the Parties), *provided* that [***].

(e) **Indemnification.** For clarity, Denali agrees to indemnify the Sanofi Indemnitees and defend and hold each of them harmless, from and against any and all Indemnified Losses in connection with any and all Third Party Claims incurred or rendered against the Sanofi Indemnitees arising from or occurring as a result of the Development, Manufacture, Commercialization or other Exploitation of any Terminated Denali Product in the Terminated Area in accordance with **Section 12.2** (Indemnification of Sanofi) after the effective date of termination, and any such termination by Denali shall not limit Denali's obligation to indemnify Sanofi for any such Third Party Claims made by such Third Party related to the Exploitation of any Terminated Denali Product after the effective date of termination.

(f) **Cooperation**. Without limiting the foregoing, each Party shall use Commercially Reasonable Efforts to cooperate with the other Party to effect a smooth and orderly transition in the Terminated Portions in the Terminated Area in a prompt and expeditious manner in accordance with the terms of this Agreement. If Sanofi has entered into contracts that solely pertain to one or more Terminated Denali Product(s) with Third Parties whose services are reasonably necessary for Denali to assume responsibility for the Terminated Denali Product(s) in

the Terminated Area and corresponding activities, then Sanofi shall, to the extent reasonably possible and requested in writing by Denali, assign all of such Third Party contracts to Denali.

13.8.3 Grant of Rights. Without limiting **Section 13.8.1** (Effects of Termination by Sanofi for Convenience or Safety or by Denali for Cause on Terminated Denali Products) and **Section 13.8.2** (Effects of Termination by Sanofi for Cause on Terminated Denali Products), Denali grants to Sanofi, its Affiliates or its Sublicensees (as the case may be) any licenses or Rights of Reference under any Denali Technology, Denali Trademarks and Denali's Corporate Name reasonably necessary for Sanofi, its Affiliates or its Sublicensees to fulfill the obligations set forth in **Section 13.8.1** (Effects of Termination by Sanofi for Convenience or Safety or by Denali for Cause on Terminated Denali Products) or **Section 13.8.2** (Effects of Termination by Sanofi for Cause on Terminated Denali Products) in the Terminated Area.

13.8.4 Effects of Termination on Terminated Sanofi Products. Solely with respect to (x) the Sanofi CNS Compounds, Sanofi CNS Products, Sanofi Peripheral Compounds, and Sanofi Peripheral Products; and (y) any compound that is not a CNS Penetrant Compound and is Covered by a Joint Program Patent claiming the composition of such compound that is not a CNS Penetrant Compound (and products containing the same), in each case, within the Terminated Portion(s) and Terminated Area (such Compounds and Products, "**Terminated Sanofi Products**"):

(a) **Termination for Convenience, Safety, Denali Material Breach, Denali Insolvency** [***]. Upon any termination by Sanofi pursuant to **Section 13.3** (For Convenience) or **Section 13.6** (Termination for Safety) or termination by Sanofi pursuant to **Section 13.2** (Termination for Material Breach), **Section 13.4** (Termination for Insolvency) [***], the following will apply:

(i) **Reversion.** All of Denali's rights under this Agreement with respect to Terminated Sanofi Products terminate and revert to Sanofi, except as provided in this **Section 13.8.4(a)** (Termination for Convenience, Safety, Denali Material Breach, Denali Insolvency [***].

(ii) **New Licenses**. [***]:

(A) [***].

(B) Sanofi may terminate its license under Denali Unblocking Know-How and Denali Unblocking Patent Rights pursuant to **Section 13.8.4(a)(ii)** with respect to one or more Terminated Sanofi Products or any country within the Terminated Area by so notifying Denali in writing, in which case the terminated Denali Unblocking Know-How and Denali Unblocking Patent Rights, respectively, shall be excluded from such license and Sanofi shall have no obligation to reimburse any Third Party payments (or abide by other Third Party obligations) under **Section 13.8.4(a)(ii)(A)** with respect to such Patent or Information to the extent so excluded.

(iii) **Regulatory Materials and Trademarks.** Denali shall assign to Sanofi (or its designee) all Regulatory Documentation Controlled by Denali or its Affiliates for the Terminated Sanofi Products and in the Terminated Area. Unless otherwise required by

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Applicable Law or requested by Sanofi, the foregoing assignment (or availability) shall be made within [***] after the effective date of such termination of this Agreement, and if such assignment cannot be made under Applicable Law within such period, as soon as practicable thereafter. Pending transfer of such Regulatory Approvals and Regulatory Documentation for the Terminated Sanofi Products in the Terminated Area, Denali hereby grants to Sanofi (or its designee(s)) a Right of Reference to all such Regulatory Approvals and Regulatory Documentation for all uses in connection with Terminated Sanofi Products. Denali shall provide the applicable Regulatory Authority a letter confirming this Right of Reference at any time within [***] after Sanofi's request and shall take such other actions and execute such other documents as Sanofi may reasonably request to further confirm and give effect to this Right of Reference. Notwithstanding the definition of Confidential Information, all such Regulatory Documentation and Regulatory Approvals in the Terminated Area for the Terminated Sanofi Products and all Joint Program Know-How that is solely specific to the Terminated Sanofi Products shall be deemed to be the Confidential Information of Sanofi and not Denali, following Denali's assignment of such Regulatory Documentation and Regulatory Approvals to Denali pursuant to this **Section 13.8.4(a)(iii)**.

(iv) **Technology Transfer.** Denali shall provide to Sanofi the Denali Unblocking Know-How (to the extent licensed under **Section 13.8.4(a)(ii)** (New Licenses)), Regulatory Documentation, Clinical Data and other Information pertaining to the Terminated Sanofi Products in the Terminated Area (to the extent such items exist as of the date of such termination), and Sanofi shall have the right to use and disclose the same in connection with the Exploitation of the Terminated Sanofi Products. Denali shall have no obligation to translate any such Denali Know-How, Regulatory Documentation, Clinical Data or other Information into English or any other language.

(v) **Transition Assistance**. The following shall also apply:

(A) **Development**. In the event Denali is conducting (or is having conducted on its behalf) any on-going Clinical Studies or non-clinical studies pertaining to any Terminated Sanofi Product in the Terminated Area, following the effective date of such termination, Denali agrees, at Sanofi's request, (A) except to the extent Sanofi terminated this Agreement in accordance with **Section 13.6** (Termination for Safety) due to a Terminated Sanofi Product and in such case, solely with respect to the Terminated Sanofi Product(s) that caused such termination, to continue to conduct or transition to Sanofi (or its designee(s)) the conduct of such studies or activities within [***] ("**Sanofi Development Wind-Down Period**") after the effective date of such termination (to the extent permitted by Applicable Law and not reasonably be expected to have a material adverse effect on patient safety); or (B) to terminate such Clinical Studies, non-clinical studies, or portions thereof (*provided* that such termination would not be inconsistent with Denali's ethical obligations (as reasonably determined by Denali pursuant to its procedures then in effect consistently applied). Notwithstanding the foregoing, Sanofi shall reimburse Denali's reasonable Out-of-Pocket Costs and FTE Costs incurred in the conduct of its obligations under this **Section 13.8.4(a)(v)(A)**; subject to Denali providing to Sanofi an invoice (and reasonable supporting evidence) for such Out-of-Pocket Costs and FTE Costs; *provided* that if the applicable termination was by Sanofi pursuant to **Section 13.2** (Termination for Material Breach), **Section 13.4** (Termination for Insolvency) [***], then Denali would be responsible for its own reasonable Out-

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of-Pocket Costs and FTE Costs incurred during the first [***] of the Sanofi Development Wind-Down Period.

(B) **Commercialization**. If at the effective time of such termination, Denali or its Affiliates are undertaking Detailing or MSL Activities with respect to a particular Terminated Sanofi Product that is a CNS Product in any country within the Terminated Area, then, at Sanofi's request, the Parties will negotiate and agree upon a plan for the orderly wind down of such activities for a period not to exceed [***]. Any FTE Costs or Out-of-Pocket Costs incurred by Denali or its Affiliates pursuant to such plan for the wind down of Denali's activities shall be reimbursed by Sanofi; subject to Denali providing to Sanofi an invoice (and reasonable supporting evidence) for such Out-of-Pocket Costs and FTE Costs.

(vi) **Financial Obligations.** Except in the case of (x) termination by Sanofi of this Agreement in its entirety or with respect to a Program in accordance with **Section 13.2** (Termination for Material Breach), or (y) termination of this Agreement in its entirety by Sanofi in accordance with **Section 13.4** (Termination for Insolvency) [***], if this Agreement is terminated in its entirety or with respect to a Program in any Terminated Area, then Sanofi's financial obligations to Denali under **Article 7** (Payments) with respect to any Terminated Sanofi Products shall survive termination and remain in effect; provided, however, that (i) [***]; and (ii) [***]. For clarity, [***], Sanofi shall continue to be obligated under **Section 13.8.4(a)(ii)(A)** to reimburse Denali for amounts payable to Third Parties under any Third Party agreements with respect to the Patents or Information that are the subject of the licenses granted by Denali to Sanofi under **Section 13.8.4(a)(ii)** (New Licenses).

(b) **Termination for Sanofi Material Breach, Sanofi Insolvency** [***]**.** Upon any Termination by Denali pursuant to **Section 13.2** (Termination for Material Breach), **Section 13.4** (Termination for Insolvency) [***], the following will apply:

(i) All of Denali's rights under this Agreement with respect to Terminated Sanofi Products terminate and revert to Sanofi, except as provided in this **Section 13.8.4(b)**.

(ii) **Section 13.8.4(a)(iii)** (Regulatory Materials and Trademarks) shall apply, *mutatis mutandis*.

(iii) **Section 13.8.4(a)(vi)** (Financial Obligations) shall apply *mutatis mutandis*;

(iv) **Transition Assistance.** With respect to the post-termination wind down and transfer to Sanofi of Clinical Studies or Co-Commercialization Activities being conducted by or under the authority of Denali in the Terminated Area as of the date of termination, Denali will provide (or cause to be provided) reasonable transition assistance to Sanofi (or its designee(s)), at the applicable FTE Rate for Denali's services in connection with such transition, for a period of no more than [***] after the effective date of such a termination (unless such period is extended by the agreement of the Parties), *provided* that [***].

(c) **Grant of Rights**. Without limiting **Section 13.8.4(a)** (Termination for Convenience, Safety, Denali Material Breach, Denali Insolvency [***]) or **Section 13.8.4(b)** (Termination for Sanofi Material Breach, Sanofi Insolvency [***]), Sanofi grants to Denali and its Affiliates any licenses or Rights of Reference under any Sanofi Technology, Sanofi Trademarks and Sanofi's Corporate Names reasonably necessary for Denali and its Affiliates to fulfill the obligations set forth in **Section 13.8.4(a)** (Termination for Convenience, Safety, Denali Material Breach, Denali Insolvency [***]) or **Section 13.8.4(b)** (Termination for Sanofi Material Breach, Sanofi Insolvency [***]), as applicable.

(d) **Indemnification**. For clarity, Sanofi agrees to indemnify the Denali Indemnitees and defend and hold each of them harmless, from and against any and all Indemnified Losses in connection with any and all Third Party Claims incurred or rendered against the Denali Indemnitees arising from or occurring as a result of the Development, Manufacture, Commercialization or other Exploitation of any Terminated Denali Product in the Terminated Area in accordance with **Section 12.1** (Indemnification of Denali) after the effective date of termination, and any such termination of this Agreement (in its entirety, or with respect to a Terminated Portion or Terminated Area) shall not limit Sanofi's obligation to indemnify Denali for any such Third Party Claims made by such Third Party related to the Exploitation of any Terminated Sanofi Product after the effective date of termination.

13.9 Remedies. Except as otherwise expressly provided herein, termination of this Agreement (either in its entirety or with respect to a Program, Product or Terminated Area) in accordance with the provisions hereof shall not limit remedies that may otherwise be available in law or equity.

13.10 Accrued Rights; Surviving Obligations.

13.10.1 Accrued Rights; Survival. Termination or expiration of this Agreement (either in its entirety or with respect to a Program, Product (and all Compounds included therein) or Terminated Area) for any reason shall not relieve a Party from any obligations that accrued prior to such termination or expiration. All rights and obligations of the Parties under this Agreement shall terminate on any expiration or termination of this Agreement in its entirety, except those described in the following provisions of this Agreement: [***] shall survive the termination or expiration of this Agreement [***].

13.10.2 Terminated Portions and Area. If this Agreement is terminated with respect to a Program or Product or Terminated Area but not in its entirety, then following such termination, the provisions of this Agreement specified in **Section 13.10.1** (Accrued Rights; Survival) shall remain in effect with respect to such terminated Program or Product or Terminated Area (to the extent such provisions would survive and apply in the event this Agreement expires or is terminated in its entirety), and all provisions not surviving in accordance with the foregoing shall terminate upon termination of this Agreement with respect to such terminated Program or Product or Terminated Area and be of no further force and effect (and, for purposes of clarity, all provisions of this Agreement shall remain in effect with respect to any Program, Compound, Product or region that is not a terminated Program or Product or Terminated Area).

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13.11 Rights in Bankruptcy. All rights and licenses granted under or pursuant to this Agreement are intended to be, and shall otherwise be deemed to be, licenses of rights to "intellectual property" as defined under Section 101(35A) of the Bankruptcy Code for purposes of Section 365(n) of the United States Bankruptcy Code ("**Bankruptcy Code**") or any analogous provisions in any other country or jurisdiction. The Parties agree that the licensee of such intellectual property under this Agreement shall retain, and may fully exercise, all of its rights and elections under the Bankruptcy Code, or any analogous provisions in any other country or jurisdiction. If a bankruptcy proceeding is commenced by or against either Party under the Bankruptcy Code or any analogous provisions in any other country or jurisdiction, the non-debtor Party shall be entitled to a complete duplicate of (or complete access to, as appropriate) any intellectual property licensed hereunder, and embodiments of such intellectual property, which, if not already in the non-debtor Party's possession, shall be delivered to the non-debtor Party within [***] of such request; *provided* that the debtor Party is excused from its obligation to deliver such intellectual property to the extent the debtor Party continues to perform all of its obligations under this Agreement and this Agreement has not been rejected pursuant to the Bankruptcy Code or any analogous provision in any other country or jurisdiction.

ARTICLE 14
HSR COMPLIANCE

14.1 HSR Act Compliance. Notwithstanding anything to the contrary in this Agreement, this Agreement is binding upon the Parties as of the Execution Date to the extent permitted by the HSR Act, but the provisions of **Article 2** (Collaboration Management) through **Article 8** (Intellectual Property) (other than **Section 8.1** (Ownership of Intellectual Property)) and **Article 9** (Pharmacovigilance and Safety) shall not take effect until the Effective Date. As used herein, the "**HSR Clearance Date**" means such time as: (a) the Parties shall have complied with all applicable requirements of the HSR Act; (b) the waiting period under the HSR Act shall have expired or been terminated early; (c) the Parties are under no antitrust-related obligation to refrain from consummating the transaction under a timing agreement entered into with a reviewing governmental authority that prevents closing without certain notice; (d) no judicial or administrative proceeding opposing consummation of all or any part of this Agreement is pending; (e) no injunction (whether temporary, preliminary or permanent) prohibiting consummation of the transactions contemplated by this Agreement or any material portion hereof is in effect; and (f) no requirements or conditions shall have been formally requested or imposed by the DOJ or FTC in connection therewith that are not reasonably and mutually satisfactory to the Parties (collectively, the "**HSR Conditions**"). In the event that the HSR Conditions are not met within [***], then either Party may terminate this Agreement upon notice, in which case, notwithstanding any provisions that are stated to survive under **Section 13.10** (Accrued Rights; Surviving Obligations), all provisions of this Agreement shall terminate and be of no force or effect whatsoever, except only that any liability of either Party for failing to comply with this **Section 14.1** shall survive.

14.2 HSR Filing. Both Parties shall promptly file following the Execution Date (and in any event, within [***] after the Execution Date) their respective pre-merger notification and report forms with the United States Federal Trade Commission ("**FTC**") and the United States Department

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of Justice ("**DOJ**") pursuant to the HSR Act, which forms shall specifically request early termination of the initial HSR Act waiting period.

14.3 Cooperation.

14.3.1 Efforts. The Parties shall use diligent efforts to promptly obtain clearance required under the HSR Act for the consummation of this Agreement and the transactions contemplated hereby and shall keep each other apprised of the status of any communications with, and any inquiries or requests for additional information from, the FTC and the DOJ and shall comply promptly with any such inquiry or request; *provided*, *however*, that neither Party shall be required to consent to the Divestiture, sale, license or other disposition or holding separate of any of its or its Affiliates' assets or to consent to any other structural or conduct remedy, and each Party and its Affiliates shall have no obligation to contest, administratively or in court, any ruling, order or other action of the FTC or DOJ or any Third Party respecting the transactions contemplated by this Agreement.

14.3.2 Solving Issues; Costs. The Parties shall instruct their respective counsel to cooperate with each other and use Commercially Reasonable Efforts [***]. In the context of this **Section 14.3.2**, diligent efforts and cooperation include counsel's undertaking: (i) to keep each other appropriately informed of communications received from and submitted to personnel of the reviewing antitrust authority; and (ii) to confer with each other regarding appropriate contacts with and response to personnel of the FTC or DOJ. [***]. Each Party shall be solely responsible for the costs and expenses of its own legal and other advice in relating to the HSR Act filing.

ARTICLE 15
MISCELLANEOUS

15.1 Force Majeure. Neither Party shall be held liable or responsible to the other Party or be deemed to have defaulted under or breached this Agreement for failure or delay in fulfilling or performing any term of this Agreement when such failure or delay is caused by or results from events beyond the reasonable control of the non-performing Party, including fires, floods, earthquakes, hurricanes, embargoes, shortages, epidemics, quarantines, war, acts of war (whether war be declared or not), terrorist acts, insurrections, riots, civil commotion, strikes, lockouts or other labor disturbances (whether involving the workforce of the non-performing Party or of any other Person) or acts, omissions or delays in acting by any governmental authority (except to the extent such delay results from the breach by the non-performing Party or any of its Affiliates of any term or condition of this Agreement), [***] (such event, a "**Force Majeure Event**"). The non-performing Party shall notify the other Party of such force majeure within [***] after such occurrence by giving written notice to the other Party stating the nature of the event, its anticipated duration, and any action being taken to avoid or minimize its effect. The suspension of performance shall be of no greater scope and no longer duration than is necessary and the non-performing Party shall use diligent efforts to remedy its inability to perform.

15.2 Export Control. This Agreement is made subject to any restrictions concerning the export of products or technical information from the United States or other countries that may be imposed on the Parties from time to time. Each Party agrees that it will not export, directly or

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indirectly, any technical information acquired from the other Party under this Agreement or any products using such technical information to a location or in a manner that at the time of export requires an export license or other governmental approval, without first obtaining the written consent to do so from the appropriate agency or other governmental entity in accordance with Applicable Law.

15.3 Assignment; Effects of Acquisitions.

15.3.1 Limited Ability to Assign Without Consent. Without the prior written consent of the other Party, neither Party shall sell, transfer, assign, delegate (except as expressly permitted under this Agreement), pledge, or otherwise dispose of, whether voluntarily, involuntarily, by operation of law or otherwise, this Agreement or any of its rights or duties hereunder; *provided* that (a) either Party may make such an assignment without the other Party's consent to (i) [***]; (ii) a [***]; or (iii) [***]. [***]. Any attempted assignment or delegation in violation of this **Section 15.3** (Assignment; Effects of Acquisition) shall be void and of no effect. All validly assigned and delegated rights and obligations of the Parties hereunder shall be binding upon and inure to the benefit of and be enforceable by and against the successors and permitted assigns of Denali or Sanofi, as the case may be. The permitted assignee or transferee shall assume all obligations of its assignor or transferor under this Agreement. Without limiting the foregoing, the grant of rights set forth in this Agreement shall be binding upon any successor or permitted assignee of a Party, and the obligations of the other Party, including the payment obligations, shall run in favor of any such successor or permitted assignee of such Party's benefits under this Agreement.

15.3.2 [***]. [***].

15.4 Severability. If any provision of this Agreement is held to be illegal, invalid or unenforceable under any present or future law, and if the rights or obligations of either Party under this Agreement will not be materially and adversely affected thereby, (a) such provision shall be fully severable; (b) this Agreement shall be construed and enforced as if such illegal, invalid or unenforceable provision had never comprised a part hereof; (c) the remaining provisions of this Agreement shall remain in full force and effect and shall not be affected by the illegal, invalid or unenforceable provision or by its severance herefrom; and (d) in lieu of such illegal, invalid or unenforceable provision, there shall be added automatically as a part of this Agreement a legal, valid, and enforceable provision as similar in terms to such illegal, invalid or unenforceable provision as may be possible and reasonably acceptable to the Parties. To the fullest extent permitted by Applicable Law, each Party hereby waives any provision of law that would render any provision hereof illegal, invalid, or unenforceable in any respect.

15.5 Governing Law, Jurisdiction and Service.

15.5.1 Governing Law. This Agreement or the performance, enforcement, breach or termination hereof shall be interpreted, governed by and construed in accordance with the laws of the State of [***], United States, excluding any conflicts or choice of law rule or principle that might otherwise refer construction or interpretation of this Agreement to the substantive law of another jurisdiction; *provided* that all questions concerning (a) determination of whether information and inventions are conceived, discovered, developed or otherwise made by a Party for

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the purpose of allocating proprietary rights (including Patent, copyright or other intellectual property rights) therein, shall, for purposes of this Agreement, be made in accordance with Applicable Law in the United States; and (b) the construction or effect of Patents shall be determined in accordance with the laws of the country or other jurisdiction in which the particular Patent has been filed or granted, as the case may be. The Parties agree to exclude the application to this Agreement of the United Nations Convention on Contracts for the International Sale of Goods.

15.5.2 Service. Each Party further agrees that service of any process, summons, notice or document sent by notice to its address and in a manner set forth in **Section 15.7** (Notices) shall be effective service of process for any action, suit or proceeding brought against it under this Agreement in any such court.

15.6 Dispute Resolution. Except for disputes resolved by the procedures set forth in **Section 2.4.5** (Joint Committee Decision Making) or **Section 15.10** (Equitable Relief) or for which either Party has final decision-making authority as provided in **Section 2.4.5** (Joint Committee Decision Making), if a dispute arises between the Parties in connection with or relating to this Agreement or any document or instrument delivered in connection herewith ("**Dispute**"), it shall be resolved pursuant to this **Section 15.6**.

15.6.1 General. If a Dispute arises, before any action or proceeding can be instituted, Notice shall be provided from one Party to the other pursuant to **Section 15.7** (Notices), detailing the nature of the dispute, and referencing this **Section 15.6.1**. Denali's CEO and Sanofi's Executive Vice President, Global R&D ("**Sanofi Senior Officer**", together with Denali's CEO, the "**Senior Officers**") shall confer in good faith on the resolution of the issue. If such officers are not able to agree on the resolution of any such issue within [***] (or such other period of time as mutually agreed by such officers) after Notice was first provided in writing, then, except as otherwise set forth in **Section 15.6.2** (Intellectual Property Disputes) or **Section 15.6.6** (Interim Relief), the Parties must engage in mandatory [***] mediation. If the Parties are unable to select a mutually satisfactory mediator, one will be assigned by JAMS. The mediator shall not be from academia. [***].

15.6.2 Intellectual Property Disputes. In the event that a Dispute arises with respect to the validity, scope, enforceability, inventorship or ownership of any Patent, Trademark or other intellectual property rights, and such Dispute cannot be resolved in accordance with **Section 15.6.1** (General), unless otherwise agreed by the Parties in writing, such Dispute shall not be submitted to an ADR proceeding in accordance with **Section 15.6.3** (ADR), nor for resolution pursuant to **Section 15.6.6** (Interim Relief), and instead, either Party may initiate litigation in a court of competent jurisdiction, notwithstanding **Section 15.5** (Governing Law, Jurisdiction and Service), in any country or other jurisdiction in which such rights apply.

15.6.3 ADR.

(a) Except as otherwise expressly provided in **Section 15.6.2** (Intellectual Property Disputes) or **Section 15.6.6** (Interim Relief), and subject to **Section 15.6.1** (General), any dispute, claim or controversy arising out of or relating to this Agreement or the breach, termination, enforcement, interpretation or validity thereof, including the determination of

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the scope or applicability of this agreement to arbitrate, shall be determined by arbitration in accordance with this **Section 15.6.3**. The arbitration shall be conducted in English and shall be administered by JAMS pursuant to its Comprehensive Arbitration Rules and Procedures. If the amount in controversy is less than [***], the JAMS Streamlined Arbitration Rules and Procedures shall be followed.

(b) The arbitration shall be conducted by a panel of three (3) arbitrators (each, an "**Arbitrator**", and collectively, the "**Arbitrators**"). No Arbitrator shall be from academia. If the Parties are unable to agree on the Arbitrators, JAMS shall designate the Arbitrators. The Arbitrators may engage one or more independent experts with experience in the subject matter of the dispute to advise the Arbitrators, but final decision making authority shall remain with the Arbitrators.

(c) Notwithstanding the JAMS Comprehensive Arbitration Rules and Procedures, and unless otherwise agreed to by both Parties:

(i) the total duration of the arbitration proceeding shall not last more than [***]from filing the Notice of Claim until the [***] day of the arbitration hearing.

(ii) Fact discovery shall be limited to [***] custodial document productions per Party and [***] fact depositions per Party. Expert discovery shall be limited to [***] experts per Party and [***] expert depositions per Party. Each Party can submit up to [***] expert reports, no more than [***] pages each.

(iii) Each Party may submit one pre-trial brief of no more than [***] pages, and there will be no other briefing or motion practice. Any arbitration hearing shall not exceed [***]. Each Party can call no more than [***] fact witnesses and [***] expert witnesses. Direct testimony per witness shall not exceed [***], and cross examination of any fact witness shall not exceed [***]. The Arbitrators' decision must be issued within [***] of the [***] day of the hearing, and the Arbitrators' decision cannot exceed [***].

(d) The Parties agree that the decision of the Arbitrators shall be the binding remedy between them regarding the dispute presented to the Arbitrators. Unless otherwise mutually agreed upon by the Parties, the arbitration proceedings shall be conducted in [***]. The Parties agree that they shall share equally the cost of the arbitration filing and hearing fees, the cost of the independent expert retained by the Arbitrators and the cost of the Arbitrators and administrative fees of JAMS. Each Party shall have the right to be represented by counsel in all aspects of any ADR proceeding and each Party shall bear its own costs, attorneys' and witnesses' fees and associated costs and expenses.

(e) Settlement negotiations, including any statements made therein, shall not be admissible under any circumstances. Affidavits prepared for purposes of the ADR hearing also shall not be admissible. As to all other matters, the panel shall have sole discretion regarding the admissibility of any evidence. Except as necessary for enforcement of the final award, or as required by law, the existence of the dispute, any settlement negotiations, the ADR proceeding, any submissions (including exhibits, testimony, proposed rulings, and briefs), and the rulings shall

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be deemed to be Confidential Information of both Parties under **Article 10** (Confidentiality and Non-Disclosure). The panel shall have the authority to impose sanctions for unauthorized disclosure of Confidential Information.

15.6.4 Disputes Regarding [***]. In the event of a Dispute as to whether [***], then either Party may, on written notice to the other Party, refer such matter to an independent Third Party laboratory, acceptable to the other Party (such acceptance not to be unreasonably withheld, conditioned or delayed) ("**Independent Third Party Lab**"). Such Independent Third Party Lab shall perform [***], as applicable, and provide to both Parties a written report summarizing the results of such tests and the Independent Third Party Lab's conclusion as to [***]. The conclusions of the Independent Third Party Lab shall be final and binding on the Parties and the Parties shall share equally the costs of any Independent Third Party Lab engaged by a Party pursuant to this **Section 15.6.4**.

15.6.5 Expert Arbitration. Any Dispute expressly stated in this Agreement to be resolved pursuant to this **Section 15.6.5** [***] shall take place pursuant to the following procedures.

(a) The expert arbitration shall be overseen by and conducted as a "baseball" form of binding arbitration by the panel selected in accordance with the procedure set forth in **Section 15.6.3(b)**, and conducted pursuant to JAMS rules as provided in **Section 15.6.3** (ADR), except as modified under this **Section 15.6.5**. The panel may, upon agreement by the Parties, modify the procedures under this **Section 15.6.5** and the JAMS rules, as appropriate solely to expedite a "baseball" arbitration. The hearing to resolve each of the issues identified by the parties in the Parties shall be had no later than [***] after selection of the expert panel described in **Section 15.6.5(b)**.

(b) Promptly following receipt of any notice requiring dispute resolution pursuant to this **Section 15.6.5**, the panel may engage one or more experts to assist the panel in resolving the issue under the supervision of the panel as provided in **Section 15.6.5(a)**, which experts shall be neutral and independent of both Parties and all of their respective Affiliates, shall have significant experience and expertise in the substantive area in question, and shall have some experience in mediating or arbitrating issues relating to such agreements. Any legal questions referred to the experts or raised by an expert shall be resolved by the panel.

15.6.6 Interim Relief. Notwithstanding anything herein to the contrary, nothing in this **Section 15.6** (Dispute Resolution) shall preclude either Party from seeking interim or provisional relief, including a temporary restraining order, preliminary injunction or other interim equitable relief concerning a Dispute, if necessary to protect the interests of such Party. This **Section 15.6.6** shall be specifically enforceable.

15.7 Notices.

15.7.1 Notice Requirements. Any notice, request, demand, waiver, consent, approval or other communication permitted or required under this Agreement shall be in writing, shall refer specifically to this Agreement and shall be deemed given only if (a) delivered by hand;

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(b) sent by facsimile or other reliable electronic transmission (with complete transmission confirmed); or (c) sent by internationally recognized overnight delivery service that maintains records of delivery, addressed to the Parties at their respective addresses specified in **Section 15.7.2** (Address for Notice) or to such other address as the Party to whom notice is to be given may have provided to the other Party in accordance with this **Section 15.7** (Notices). Such notice shall be deemed to have been given as of the date delivered by hand or transmitted by facsimile or other electronic transmission (with complete transmission confirmed) or on the [***] (at the place of delivery) after deposit with an internationally recognized overnight delivery service. Any notice delivered by facsimile or other electronic transmission shall be confirmed by a hard copy delivered as soon as practicable thereafter by the method described in clause (c) above. This **Section 15.7** (Notices) is not intended to govern the day-to-day business communications necessary between the Parties in performing their obligations under the terms of this Agreement.

15.7.2 Address for Notice.

If to Sanofi, to:

Genzyme Corporation
50 Binney Street
Cambridge, MA 02142
[***]

with a further copies (which shall not constitute notice) to:

Sanofi
50 Binney Street
Cambridge, MA 02142
[***]

Jones Day
4655 Executive Drive, Suite 1500
San Diego, California 92121
[***]

If to Denali, to:

Denali Therapeutics Inc.
151 Oyster Point Blvd
South San Francisco, CA 94080
[***]

with a copy (which shall not constitute notice) to:

Wilson Sonsini Goodrich and Rosati P.C.
12235 El Camino Real, Suite 200
San Diego, California 92130
[***]

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15.8 Entire Agreement; Amendments. This Agreement, together with the Schedules attached hereto, sets forth and constitutes the entire agreement and understanding between the Parties with respect to the subject matter hereof and all prior agreements, understandings, promises and representations, whether written or oral, with respect thereto are superseded hereby (including that certain Confidentiality Agreement between the Parties or their respective Affiliates dated [***], as amended, and, for the avoidance of doubt, drafts of the Non-Binding Term Sheet for Discussion Purposes Only exchanged between the Parties prior to the Execution Date). Each Party confirms that it is not relying on any representations or warranties of the other Party except as specifically set forth in this Agreement. Except for amendments and modifications to the Development Plans, Commercialization Plans and Co-Commercialization Plans in accordance with **Article 2** (Collaboration Management) and **Section 5.3.3** (Amendments and Updates), no amendment, modification, release or discharge shall be binding upon the Parties, unless in writing and duly executed by authorized representatives of both Parties.

15.9 English Language. This Agreement shall be written and executed in, and all other communications under or in connection with this Agreement shall be in, the English language. Any translation into any other language shall not be an official version thereof, and in the event of any conflict in interpretation between the English version and such translation, the English version shall control.

15.10 Equitable Relief. Each Party acknowledges and agrees that the restrictions set forth in [***] are reasonable and necessary to protect the legitimate interests of the other Party and that such other Party would not have entered into this Agreement in the absence of such restrictions, and that any breach or threatened breach of any provision of such Section or Articles may result in irreparable injury to such other Party for which there may be no adequate remedy at law. In the event of a breach or threatened breach of any provision of such Section or Articles, the Non-Breaching Party shall be authorized and entitled to seek from any court of competent jurisdiction injunctive relief, whether preliminary or permanent and specific performance. Nothing in this **Section 15.10** is intended, or should be construed, to limit either Party's right to equitable relief or any other remedy for a breach of any other provision of this Agreement.

15.11 Waiver and Non-Exclusion of Remedies. Any term or condition of this Agreement may be waived at any time by the Party that is entitled to the benefit thereof, but no such waiver shall be effective, unless set forth in a written instrument duly executed by or on behalf of the Party waiving such term or condition. The waiver by either Party hereto of any right hereunder or of the failure to perform or of a breach by the other Party shall not be deemed a waiver of any other right hereunder or of any other breach or failure by such other Party whether of a similar nature or otherwise. The rights and remedies provided herein are cumulative and do not exclude any other right or remedy provided by Applicable Law or otherwise available except as expressly set forth herein.

15.12 No Benefit to Third Parties. Except as provided in **Article 12** (Indemnity; Limitations of Liability; Insurance) and **Section 6.5.1** (Existing Denali In-License Agreements), covenants and agreements set forth in this Agreement are for the sole benefit of the Parties hereto,

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and successors and permitted assigns of the Parties, and shall not be construed as conferring any rights on any other Persons.

15.13 Further Assurance. Each Party shall duly execute and deliver, or cause to be duly executed and delivered, such further instruments and do and cause to be done such further acts and things, including the filing of such assignments, agreements, documents and instruments, as may be necessary or as the other Party may reasonably request in connection with this Agreement or to carry out more effectively the provisions and purposes hereof, or to better assure and confirm unto such other Party its rights and remedies under this Agreement.

15.14 Relationship of the Parties. It is expressly agreed that Denali, on the one hand, and Sanofi, on the other hand, shall be independent contractors and that the relationship between the Parties shall not constitute a partnership, joint venture or agency, including for all tax purposes; [***]. Except to the extent expressly stated in this Agreement, neither Denali, on the one hand, nor Sanofi, on the other hand, shall have the authority to make any statements, representations or commitments of any kind, or to take any action, which shall be binding on the other, without the prior written consent of the other Party to do so. All persons employed by a Party shall be employees of such Party and not of the other Party and all costs and obligations incurred by reason of any such employment shall be for the account and expense of such Party.

15.15 Performance by Affiliates, Sublicensees and Third Party Providers. Each Party may use one (1) or more of its Affiliates, Sublicensees or Third Party Providers to exercise such Party's rights or perform its obligations and duties hereunder. In such event: (a) [***]; (b) [***]; and (c) [***].

15.16 Counterparts; Execution. This Agreement may be executed in two (2) or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one (1) and the same instrument. This Agreement may be executed by facsimile or electronically transmitted signatures and such signatures shall be deemed to bind each Party hereto as if they were original signatures.

15.17 References. Unless otherwise specified, (a) references in this Agreement to any Article, Section or Schedule shall mean references to such Article, Section or Schedule of this Agreement; (b) references in any Section to any clause are references to such clause of such Section; and (c) references to any agreement, instrument or other document in this Agreement refer to such agreement, instrument or other document as originally executed or, if subsequently amended, replaced or supplemented from time to time, as so amended, replaced, or supplemented and in effect at the relevant time of reference thereto.

15.18 Construction. Except where the context otherwise requires, wherever used, the singular shall include the plural, the plural the singular, the use of any gender shall be applicable to all genders and the word "or" is used in the inclusive sense (and/or). Whenever this Agreement refers to a number of days, unless otherwise specified, such number refers to calendar days. The captions of this Agreement are for convenience of reference only and in no way

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

define, describe, extend or limit the scope or intent of this Agreement or the intent of any provision contained in this Agreement. The term “including,” “include” or “includes” as used herein shall mean “including, but not limited to,” and shall not limit the generality of any description preceding such term. The language of this Agreement shall be deemed to be the language mutually chosen by the Parties and no rule of strict construction shall be applied against either Party hereto. Each Party represents that it has been represented by legal counsel in connection with this Agreement and acknowledges that it has participated in the drafting hereof. In interpreting and applying the terms and provisions of this Agreement, the Parties agree that no presumption will apply against the Party which drafted such terms and provisions. All amounts (including payment amounts and calculation thereof) are stated in U.S. Dollars unless another currency is specified.

[*SIGNATURE PAGE FOLLOWS.****]***

THIS COLLABORATION AND LICENSE AGREEMENT IS EXECUTED by the authorized representatives of the Parties as of the Execution Date.

Denali Therapeutics Inc.

By /s/ Ryan Watts:
Name: Ryan Watts
Title: CEO

Genzyme Corporation

By: /s/ Muzammil Mansuri
Name: Muzammil Mansuri
Title: Executive Vice President

Schedule 1.23(a)

[***]

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

Schedule 1.23(b)

[***]

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Schedule 1.36

[***]

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Schedule 1.40

[***]

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

Schedule 1.61

[***]

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

Schedule 1.73

[***]

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

Schedule 1.74

[***]

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

Schedule 1.75

[***]

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Schedule 1.130

[***]

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Schedule 3.3.1

[***]

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Schedule 3.3.3

[***]

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Schedule 4.1

[***]

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Schedule 5.2.4

[***]

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

Schedule 6.4

[***]

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

Schedule 6.5.1

[***]

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Schedule 7.4.1 (a)

[***]

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Schedule 7.4.1(b)

[***]

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

Schedule 8.2.1(a)

[***]

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Schedule 11.2.4

[***]

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

Schedule 11.2.11

[***]

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

Schedule 11.4.8

[***]

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

Schedule 13.3

[***]

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Exhibit 21.1

SUBSIDIARIES

Subsidiary Name	Jurisdiction of Incorporation or Organization
F-star Gamma Limited	United Kingdom

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the 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 report dated March 12, 2019, with respect to the consolidated financial statements of Denali Therapeutics Inc. in this Annual Report (Form 10-K) for the year ended December 31, 2018.

/s/ Ernst & Young LLP

Redwood City, California
March 12, 2019

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; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

    a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

    b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 12, 2019

/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; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

    a. All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

    b. Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 12, 2019

/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 period ended December 31, 2018, 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: March 12, 2019

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, 2018, 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: March 12, 2019

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