

The information in this preliminary prospectus supplement is not complete and may be changed. A registration statement relating to these securities has been filed with the Securities and Exchange Commission and is effective. This preliminary prospectus supplement and the accompanying prospectus are not an offer to sell these securities and they are not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to Completion
Preliminary Prospectus Supplement dated October 18, 2022

PROSPECTUS SUPPLEMENT
(To prospectus dated February 28, 2022)

shares



Common Stock

We are offering up to _____ shares of our common stock in this offering.

Our common stock is quoted on the Nasdaq Global Select Market under the symbol "DNLI". On October 17, 2022, the last reported sale price of our common stock on the Nasdaq Global Select Market was \$33.70 per share.

Investing in our common stock involves risks. See "[Risk Factors](#)" beginning on page [S-21](#) of this prospectus supplement.

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

	Per Share	Total
Public offering price	\$	\$
Underwriting discounts and commissions ⁽¹⁾	\$	\$
Proceeds, before expenses, to Denali Therapeutics Inc.	\$	\$

(1) We have agreed to reimburse the underwriters for certain FINRA related expenses. See "Underwriting."

The underwriters have the option to purchase _____ additional shares from us at the initial price to the public less the underwriting discount.

The underwriters expect to deliver the shares against payment in New York on or about October _____, 2022.

Goldman Sachs & Co. LLC

J.P. Morgan

Jefferies

Berenberg

Cantor

H.C. Wainwright & Co.

Prospectus supplement dated October _____, 2022.

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We have not authorized anyone to provide any information or to make any representations other than those contained or incorporated by reference in this prospectus supplement, the accompanying prospectus or in any free writing prospectuses we have prepared. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus supplement and the accompanying prospectus is an offer to sell only the shares offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. The information contained in this prospectus supplement and the accompanying prospectus is current only as of the date of the document in which it is contained.

ABOUT THIS PROSPECTUS SUPPLEMENT

This document is part of the registration statement that we filed with the Securities and Exchange Commission, or the SEC, using a "shelf" registration process and consists of two parts. The first part is this prospectus supplement, including the documents incorporated by reference, which describes the specific terms of this offering. The second part, the accompanying prospectus, including the documents incorporated by reference, gives more general information, some of which may not apply to this offering. Generally, when we refer to the "prospectus", we are referring to both parts combined. This prospectus supplement may add to, update or change information in the accompanying prospectus and the documents incorporated by reference into this prospectus supplement or the accompanying prospectus.

If information in this prospectus supplement is inconsistent with the accompanying prospectus or with any document incorporated by reference that was filed with the SEC before the date of this prospectus supplement, you should rely on this prospectus supplement. This prospectus supplement, the accompanying prospectus and the documents incorporated by reference into each include important information about us, the securities being offered and other information you should know before investing in our securities. You should also read and consider information in the documents we have referred you to in the sections of this prospectus supplement and the accompanying prospectus entitled "Where You Can Find Additional Information" and "Incorporation of Certain Information by Reference."

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference herein or into the accompanying prospectus were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

We take no responsibility for, and can provide no assurances as to the reliability of, any information that is in addition to or different from that contained or incorporated by reference in this prospectus supplement and the accompanying prospectus. We are not offering to sell these securities in any jurisdiction where the offer or sale is not permitted. You should not assume that the information contained or incorporated by reference in this prospectus supplement or the accompanying prospectus is accurate as of any date other than as of the date of this prospectus supplement or the accompanying prospectus, as the case may be, or in the case of the documents incorporated by reference, the date of such documents regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or any sale of our securities. Our business, financial condition, liquidity, results of operations and prospects may have changed since those dates.

All references in this prospectus supplement or the accompanying prospectus to "Denali," the "Company," "we," "us," or "our" mean Denali Therapeutics Inc. and our subsidiaries, unless we state otherwise or the context otherwise requires. We use Denali Therapeutics®, the Denali Therapeutics logo, and other marks as trademarks in the United States and other countries. This prospectus supplement and any free writing prospectus that we may have authorized for use in connection with this offering and the information incorporated herein or therein, as the case may be, by reference contain references to our trademarks and service marks and to those belonging to other entities. Solely for convenience, trademarks and trade names referred to in this prospectus supplement and any free writing prospectus that we may have authorized for use in connection with this offering, 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.

No action is being taken in any jurisdiction outside the United States to permit a public offering of the securities or possession or distribution of this prospectus supplement or the accompanying prospectus in that jurisdiction. Persons who come into possession of this prospectus supplement or the accompanying prospectus in jurisdictions outside the United States are required to inform themselves about and to observe any restrictions as to this offering and the distribution of this prospectus supplement or the accompanying prospectus applicable to that jurisdiction.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein and any free writing prospectus that we may have authorized for use in connection with this offering contain statements that are not historical facts and are considered forward-looking within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. All statements other than statements of historical facts contained in this prospectus, including statements regarding our future results of operations and financial position, business strategy, product candidates, planned preclinical studies and clinical trials, research and development costs, regulatory approvals, timing and likelihood of success, as well as plans and objectives of management for future operations, are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that are in some cases beyond our control and may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "would," "expect," "plan," "anticipate," "could," "intend," "target," "project," "contemplate," "believe," "estimate," "predict," "potential" or "continue" or the negative of these terms or other similar expressions. Forward-looking statements contained in this prospectus include, but are not limited to, statements about:

- the progress, success, cost and timing of our development activities, preclinical studies and clinical trials, and in particular the development of our blood-brain barrier ("BBB") platform technology, programs and biomarkers, including the initiation and completion of studies or trials and related preparatory work, enrollment in such trials, the timing of when data from clinical trials will become available, the advancement of new molecule entities into clinical development and related timing, and the filing of investigational new drug applications or clinical trial applications;
- 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 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 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;
- our potential plans and ability to develop our own manufacturing facilities;
- the pricing and reimbursement of our product candidates, if approved and commercialized;
- the success of competing products or platform technologies that are or may become available;
- our ability to attract and retain key managerial, scientific and medical personnel;
- the accuracy of our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- our ability to enhance operational, financial and information management systems;
- the impact of increasing geopolitical uncertainty, rising inflation and increased labor market competition;
- the impact of the COVID-19 pandemic, rising interest rates, and global economic and social conditions on our business;
- our financial performance; and
- the intended use of proceeds from this offering.

We have based these forward-looking statements largely on our current expectations and projections about our business, the industry in which we operate, and financial trends that we believe may affect our business, financial condition, results of operations and prospects, and these forward-looking statements are not guarantees of future performance or development. These forward-looking statements speak only as of the date of the document containing the applicable statement and are subject to a number of risks, uncertainties and assumptions described in the section titled "Risk Factors" and elsewhere in this prospectus supplement and the accompanying prospectus. Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified, you should not rely on these forward-looking statements as predictions of future events. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. Except as required by applicable law, we undertake no obligation to update publicly any forward-looking statements for any reason after the date of this prospectus supplement 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 prospectus supplement or the accompanying prospectus, as the case may be, 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 prospectus supplement and the accompanying prospectus and any free writing prospectus that we may have authorized for use in connection with this offering contain estimates, projections and other information concerning our industry, our business and the markets for our product candidates. We obtained the industry, market and similar data set forth in this prospectus supplement and the accompanying prospectus or the free writing prospectus, as the case may be, 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.

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights selected information contained elsewhere or incorporated by reference in this prospectus supplement and the accompanying prospectus and in the documents we incorporate by reference. This summary may not contain all the information that you should consider before investing in our securities. You should read this entire prospectus supplement and the accompanying prospectus carefully, especially the risks of investing in our common stock discussed under "Risk Factors" beginning on page [S-21](#) of this prospectus supplement, along with our consolidated financial statements and notes to those consolidated financial statements and the other information incorporated by reference in this prospectus supplement and the accompanying prospectus, before making an investment decision. This prospectus supplement may add to, update or change information in the accompanying prospectus.

Overview

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

We are a clinical stage biopharmaceutical company developing a broad portfolio of product candidates engineered to cross the blood-brain barrier ("BBB") for neurodegenerative and lysosomal storage diseases. We have a diversified and differentiated portfolio of both small molecule and biotherapeutic medicines, comprising seven product candidates in clinical development across six therapeutic areas as well as more than a dozen preclinical therapeutic candidates. Each of our programs has been engineered for efficient delivery across the BBB to increase drug exposure in the brain after systemic administration. We have discovered and developed a proprietary platform technology called the Transport Vehicle or "TV", which we have used in developing our portfolio of brain-penetrant therapies based on enzymes ("ETV"), antibodies ("ATV"), proteins ("PTV"), and oligonucleotides ("OTV"). We believe the combination of a clinically validated delivery platform and a maturing therapeutic portfolio will position us for long-term success in our goal to advance next-generation, targeted medicines for people living with neurodegenerative diseases. We plan to further grow our discovery and clinical development capabilities and intend to build internal manufacturing capabilities and commercial infrastructure in a staged manner that is aligned with the progression of our portfolio. Our vision is to serve patients as a fully integrated global organization.

Key Achievements Since Company Founding in 2015

- Built a broad portfolio comprised of 7 clinical-stage programs of which 3 are currently late-stage
- Entered 3 strategic collaborations totaling \$1.3 billion in upfront payments and >\$3 billion in potential milestones
- Invented and developed proprietary BBB Transport Vehicle technology with potential to deliver enzymes, antibodies, proteins and oligonucleotides via systemic administration
- Achieved preclinical proof of concept for TV-enabled brain delivery of antisense oligonucleotides
- Advanced 10 investigational new drug applications/clinical trial applications for new molecules to enter clinical development
- 20+ publications in top tier scientific journals
- 90+ patents granted worldwide
- 3 Denali women leaders awarded "Most Influential Women in the Bay Area"

We have three late-stage development programs: DNL310 (ETV:IDS) for MPS II (Hunter syndrome); BIIB122/DNL151 (LRRK2 inhibitor) for Parkinson's disease ("PD"); and SAR443820/DNL788 (CNS-penetrant RIPK1 inhibitor) for amyotrophic lateral sclerosis ("ALS"). In addition, we have initiated planning for late-stage development of DNL343 (eIF2B activator) for ALS. We are conducting first-in-human studies of TAK-920/DNL919 (ATV:TREM2) for Alzheimer's disease ("AD") and TAK-594/DNL593 (PTV:PGRN) for frontotemporal dementia-granulin ("FTD-GRN"). SAR443122/DNL758 (peripheral RIPK1 inhibitor) is in mid-stage development for cutaneous lupus erythematosus ("CLE").

As our portfolio matures and our company scales, we will maintain a deep focus on science to guide our efforts to discover, develop and deliver medicines to patients. Our discovery and development strategy is guided by three overarching principles that we believe will significantly increase the probability of success and accelerate the timing to bring effective therapeutics to people living with neurodegenerative diseases:

(1) Degenogene Pathways – each of our programs addresses a molecular target or biological pathway that is genetically validated to cause or increase the risk for neurodegenerative diseases.

(2) BBB Platform Technology – we engineer our product candidates to cross the BBB and act directly in the brain by following a rigorous approach in designing small molecules and by using our proprietary Transport Vehicle platform technology to effectively deliver large therapeutic molecules, such as enzymes, proteins, antibodies, and oligonucleotides, across the BBB after intravenous administration.

(3) Biomarker-Driven Development – we discover, develop and use biomarkers to inform dose selection, assess clinical activity, and to identify patients most likely to respond to our therapies.

Our target indications include diseases with large patient populations, such as Alzheimer's disease and Parkinson's disease, as well as rare indications, such as Hunter syndrome, FTD-GRN and ALS. We expect our first potential product launches will be in rare disease categories. Launching first in rare indications gives us the opportunity to build and establish our commercial organization so that we are poised for success in larger indications over time. Our most advanced TV-enabled program, DNL310 (ETV:IDS), is intended to replace the standard of care in Hunter syndrome, which belongs to a group of rare lysosomal storage diseases ("LSDs"). LSDs affect more than 30,000 individuals world-wide for whom central nervous system ("CNS") manifestations and many peripheral symptoms continue to remain unaddressed by current standard of care. We aim to leverage certain efficiencies of scale to support the commercialization of additional product candidates to create an LSD franchise. We are actively working toward building clinical manufacturing capabilities and continuing to expand our commercial capabilities in LSDs and intend to serve patients directly in several countries. In parallel, we are advancing our programs for rare neurodegenerative diseases, such as ALS and FTD-GRN, which impact around 500,000 individuals world-wide. We may commercialize these product candidates, if approved, independently in key markets and/or leverage partnerships to ensure optimal access for patients. For the common neurodegenerative diseases, such as AD and PD, which afflict 40 to 50 million individuals world-wide, we plan to initially leverage strategic collaborations that contribute existing global commercial infrastructure.

Collaborations and partnering are central components of our strategy to build, develop and commercialize our portfolio of product candidates. We have numerous arrangements with biopharmaceutical companies, technology companies, academic institutions, foundations, and patient-focused data companies. Notable active arrangements include those with Biogen Inc.'s subsidiaries, Biogen MA Inc. ("BIMA") and Biogen International GmbH ("BIG") (BIMA and BIG, collectively, "Biogen"), Takeda Pharmaceutical Company Limited ("Takeda"), and Genzyme Corporation, a wholly owned subsidiary of Sanofi S.A. ("Sanofi"). We hold significant development and commercialization rights to all of our CNS programs, including the programs which are subject to our collaboration agreements with Biogen, Sanofi and Takeda, where we share responsibility for clinical development and share commercialization rights in the United States and China. Our cost of developing programs associated with these collaborations are largely covered through upfront payments, expected incoming milestones and cost sharing. We may seek additional strategic partnering opportunities as we strive to capture the full value of our portfolio and platforms. For example, the TV platform has potential applications beyond our core focus on neurodegeneration (e.g., oncology, infectious disease, neuro-psychiatry, pain).

At Denali, we are guided by the core Denali values of trust, growth, grit and unity, and these values form the foundation of our Environmental, Social & Governance ("ESG") practices. Our working environment seeks to develop quality leaders, foster diversity and inclusion, and emphasize continuous growth. Denali embraces differences and acknowledges the valuable perspectives that a diverse and inclusive workforce brings to problem-solving and innovation. We strive to manage our operations in a way that is sustainable and reduces our impact on the environment. Denali has in place a Green Alternative program which provides researchers with information on suitable alternative chemicals that have a lower environmental impact for common solvents. Additionally, several waste streams have been segregated on-site for proper disposal or recycling, such as containers, food waste, plastics, styrofoam, and glass chemical containers, to maximize recycling and composting. We also maintain an ongoing commitment to corporate governance principles, with oversight of ESG matters by Denali's Board of Directors, and strong performance orientation in our compensation program.

Our Scientific Principles

(1) Degenogene Pathways

The number of genetic associations discovered in neurodegenerative diseases has grown rapidly in recent years. Degenogenes are genes that when mutated cause, or are major risk factors for, neurodegenerative diseases. Analysis of recently discovered degenogenes point to important disease pathways that, when dysregulated, increase the risk of developing neurodegenerative disease, and provide a strong scientific foundation for prioritizing drug development programs. We currently focus on programs that seek to modulate three key disease pathways:

Lysosomal Function – Dysfunction of the lysosomal system, the disposal and recycling compartment of the cell, is associated with several neurodegenerative diseases, including PD and neurodegeneration in the context of LSDs. Degenogenes linked to lysosomal function include leucine-rich repeat kinase 2 ("LRRK2"), progranulin ("PGRN"), alpha-synuclein ("aSyn"), and lysosomal enzymes, including iduronate 2-sulfatase ("IDS"), Sulfamidase ("SGSH"), and glucocerebrosidase ("GBA").

Glial Biology – Glial cells, the resident immune cells of the brain, serve various functions including supporting neuronal health, pruning neuronal synapses, and providing immune surveillance and response in the brain. Genetic and pathological data suggest that glial dysfunction significantly contributes to neurodegenerative diseases, such as Alzheimer's disease. Degenogenes that implicate immune dysfunction in the brain include triggering receptors expressed on myeloid cells 2 ("TREM2") and receptor interacting serine/threonine protein kinase 1 ("RIPK1"), a kinase downstream of the TNF receptor pathway.

Cellular Homeostasis – The brain is particularly susceptible to defects in lipid, protein or RNA homeostasis. Mutations in several ALS and FTD degenogenes alter RNA homeostasis and increase cellular stress. Eukaryotic initiation factor 2 B ("eIF2B") is an essential regulator of cellular stress, and modulators of eIF2B activity have been shown to be beneficial in numerous in vitro and in vivo models of neurodegenerative disease. Other degenogenes linked to cellular homeostasis include amyloid precursor protein ("APP"), Tau and Apolipoprotein E ("ApoE").

(2) BBB Platform Technology

Historically, the BBB has been a major challenge to the development of medicines for diseases of the Central Nervous System ("CNS"). While the BBB protects the brain from insults such as harmful substances and infections by tightly regulating transport of molecules into and out of the brain, the BBB also prevents the delivery of small-and large-molecule medicines to the brain in sufficient quantities to have therapeutic effect. We directly address the BBB challenge by engineering brain delivery for both small and large molecules.

Most small molecules are actively excluded from the brain by efflux pumps at the BBB; it has been estimated that approximately 98% do not cross the BBB. We rigorously design our small-molecule therapeutic candidates to be orally bioavailable with chemical and physical properties that enable them to be readily absorbed from the gut and to penetrate the BBB while avoiding transporter-mediated efflux.

We invented, developed, and continue to optimize a proprietary technology, called the Transport Vehicle, to deliver our large molecule biotherapeutic candidates to the brain after systemic administration. Clinical and preclinical studies with several of our TV-enabled product candidates demonstrated high concentrations and broad distribution in all explored regions of the CNS and in key CNS cell types and showed improved pharmacodynamic effects compared to standard biotherapeutics. We believe that the TV can significantly increase the probability of success of biotherapeutics for CNS indications and can enable many new potential treatment options.

Our TV technology is modular and enables several classes of biotherapeutics to more effectively cross the BBB, including enzymes, antibodies, proteins and oligonucleotides. The TV technology is engineered to engage specific BBB transport receptors, such as the transferrin receptor ("TfR"), which are highly expressed in brain capillaries and facilitate transport of proteins into the brain (**Figure 1**) in a process called receptor mediated transcytosis, or RMT.

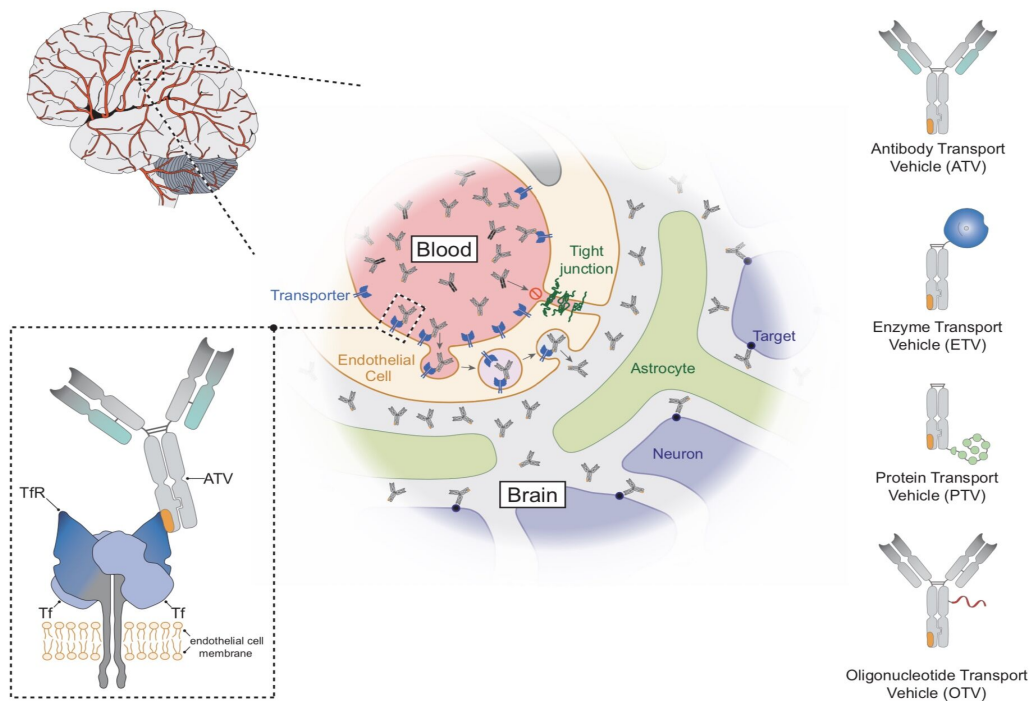


Figure 1: Engineering brain delivery. Schematic of the TV technologies, designed to cross the BBB through receptor-mediated transcytosis, leveraging endogenous receptors expressed on endothelial cells of the central nervous system vasculature.

Our pipeline of TV-enabled programs currently includes three clinical-stage programs and more than a dozen programs in preclinical development. We demonstrated clinical and preclinical proof of concept with safety and pharmacokinetic/pharmacodynamic data from the ongoing Phase 1/2 study with DNL310 (ETV:IDS) as well as data from several preclinical studies in mouse and nonhuman primate models. Preclinical studies included robust and sustained pharmacodynamic effects in the brain after intravenous dosing of TV-enabled antibodies, enzymes, proteins, and antisense oligonucleotides, while standard antibodies, enzymes, proteins and antisense oligonucleotides had no or minimal pharmacodynamic effects. These data show that TV-enabled product candidates have the potential to achieve therapeutically relevant concentrations in the brain after systemic administration, making them potentially superior to traditional biologic therapeutics in targeting neurodegenerative diseases.

Our TV technology is differentiated from other BBB technologies through its engineering approach, which may provide superior stability, safety, and higher exposure of drug candidates in the brain (**Figure 2**).

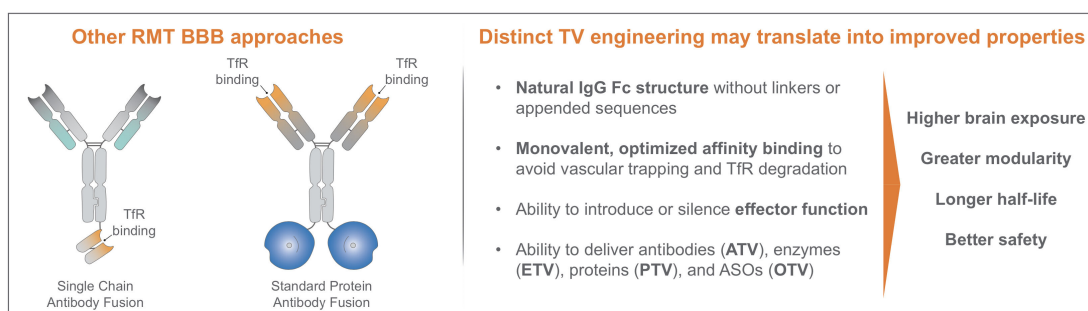
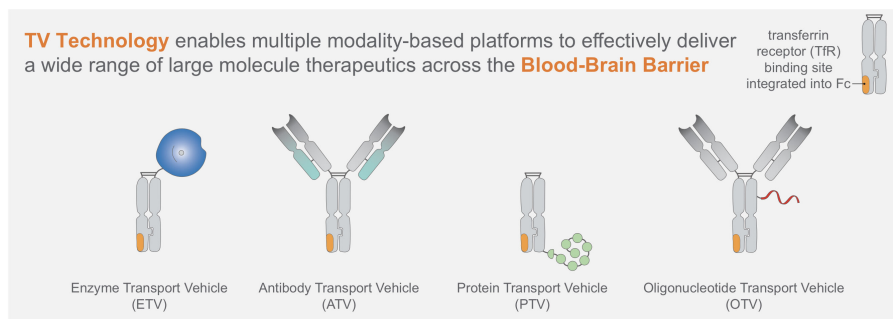


Figure 2: Denali's TV technology is modular and highly differentiated

Our most advanced program DNL310 (ETV:IDS) is currently enrolling patients in a Phase 2/3 study and we have advanced two additional TV-enabled molecules into clinical testing, namely, PTV:PGRN (TAK-594/DNL593) and ATV:TREM2 (TAK-920/DNL919). In addition, we plan to advance another ETV-enabled molecule, ETV:SGSH (DNL126) into the clinic in 2023.

We believe that we can further expand our portfolio leveraging the modularity of the TV technology. In addition to our current focus on neurodegenerative diseases and LSDs, we are exploring programs in oncology (ATV:HER2) and infectious diseases as well as other neurological and neuromuscular indications (**Figure 3**). We may develop these additional programs ourselves in the future or seek partnerships.

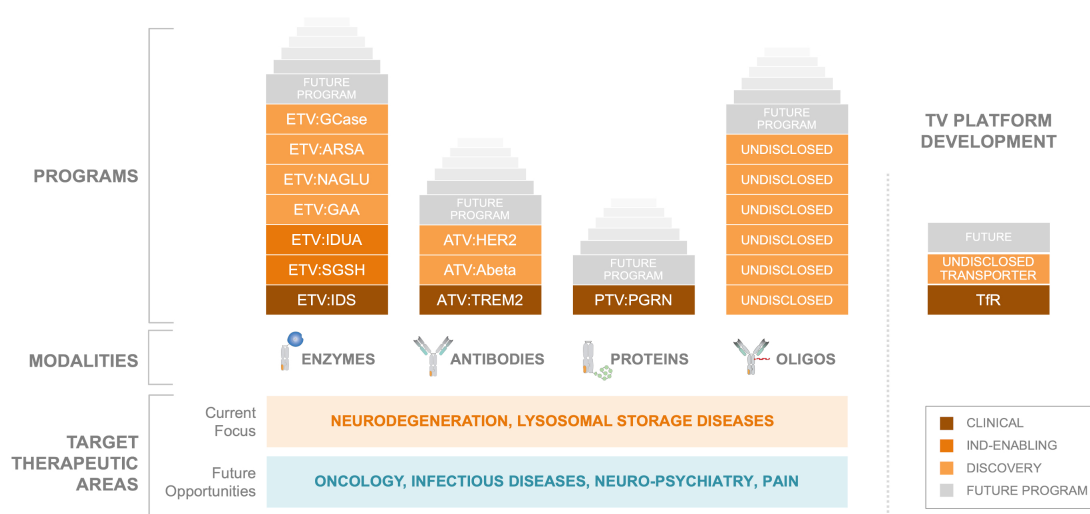


Figure 3: Denali's TV technology provides opportunities for platform expansion

(3) Biomarker-Driven Development

As part of our strategy, we identify and validate biomarkers which are relevant for both animal models and human trials and are critical for selecting patients, predicting and measuring target engagement, supporting dose selection and enabling decisions on progression of product candidates to the next phase of development. When practicable, we are developing patient selection biomarkers for our programs to enable identification of patients with the relevant disease biology and stage of disease likely to benefit from targeted therapy in order to increase the likelihood of success of clinical trials. Ultimately, we expect to positively impact market acceptance of these targeted therapies driven by high and meaningful response rates within the targeted population as defined by the patient selection biomarkers. In certain indications, regulatory approval may limit the market of a product candidate to target patient populations when patient selection biomarkers are used. In these indications, regulatory authorities may require us to run additional clinical trials prior to expanding the label for approval that includes a broader patient population.

Our Programs

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

MODALITY	TARGET	BIOLOGY	DRUG CANDIDATE	DISEASE INDICATION	DEVELOPMENT STAGE			PARTNER
					IND-Enabling	Early Clinical	Mid/Late Clinical	
LARGE MOLECULE (TV-ENABLED)	Iduronate 2-Sulfatase	Lysosomal Function	DNL310	MPS II (Hunter)	[Progress Bar]			
	PGRN	Lysosomal Function	TAK-594 (DNL593)	Frontotemporal Dementia	[Progress Bar]			Takeda
	TREM2	Glial Biology	TAK-920 (DNL919)	Alzheimer's	[Progress Bar]			Takeda
	Sulfamidase	Lysosomal Function	DNL126	MPS IIIA (Sanfilippo)	[Progress Bar]			
	Alpha-L-iduronidase	Lysosomal Function	DNL622	MPS I (Hurler)	[Progress Bar]			
	Undisclosed	Cellular Homeostasis	OTV:Undisclosed	Undisclosed	[Progress Bar]			
SMALL MOLECULE	LRRK2	Lysosomal Function	BIIB122 (DNL151)	Idiopathic Parkinson's LRRK2+ Parkinson's	[Progress Bar]			Biogen
	RIPK1 (CNS)	Glial Biology	SAR443820 (DNL788)	ALS, MS, Alzheimer's	[Progress Bar]			sanofi
	RIPK1 (Peripheral)	Other	SAR443122 (DNL758)	Cut. Lupus Eryth. (CLE) Ulcerative Colitis (UC)	[Progress Bar]			sanofi
	eIF2B	Cellular Homeostasis	DNL343	ALS, FTD	[Progress Bar]			

Small Molecules Biotherapeutics

Figure 4: Denali's current clinical pipeline

We are developing a broad portfolio of targeted therapeutic candidates for neurodegenerative diseases. Our programs are at different stages of clinical and preclinical development. In addition to our current clinical development portfolio, we expect to advance at least three new molecule entities (“NMEs”) into clinical development in the 2023 to 2025 timeframe. We discuss our most advanced programs in further detail below.

Our Transport Vehicle (TV)-Enabled Programs

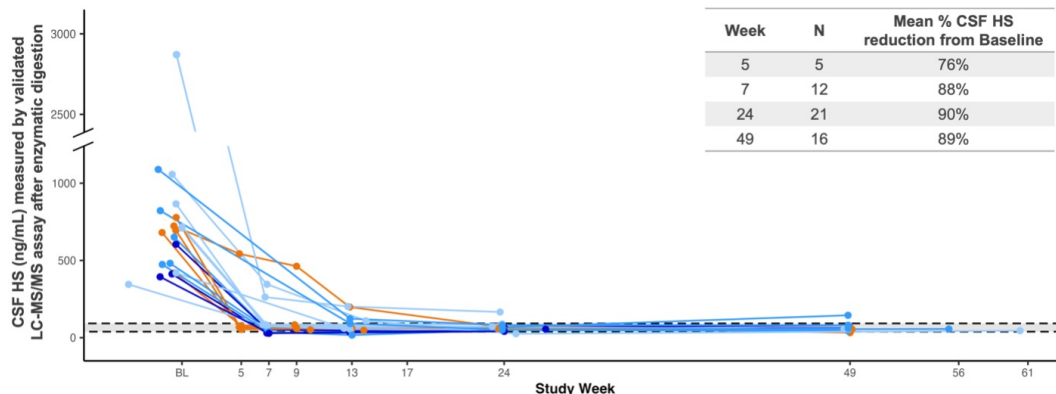
DNL310 ETV:IDS Enzyme Replacement Therapy Program for Hunter Syndrome

DNL310 (ETV:IDS) is an intravenously administered enzyme replacement therapy biotherapeutic enabled by our enzyme transport vehicle (ETV), designed to restore IDS, and reduce glycosaminoglycans (“GAGs”), including heparan sulfate, both peripherally and in the brain, in patients with mucopolysaccharidosis II, also known as MPS II, or Hunter syndrome. The product candidate is designed to address the cognitive, behavioral, and physical manifestations of Hunter syndrome. Current enzyme replacement therapy (“ERT”) only partially addresses physical manifestations of MPS II.

We are conducting an ongoing Phase 1/2 trial for DNL310 in patients with Hunter syndrome as a multicenter, multiregional, open-label trial to assess the safety, pharmacokinetics, and pharmacodynamics of DNL310 administered once weekly by intravenous infusion.

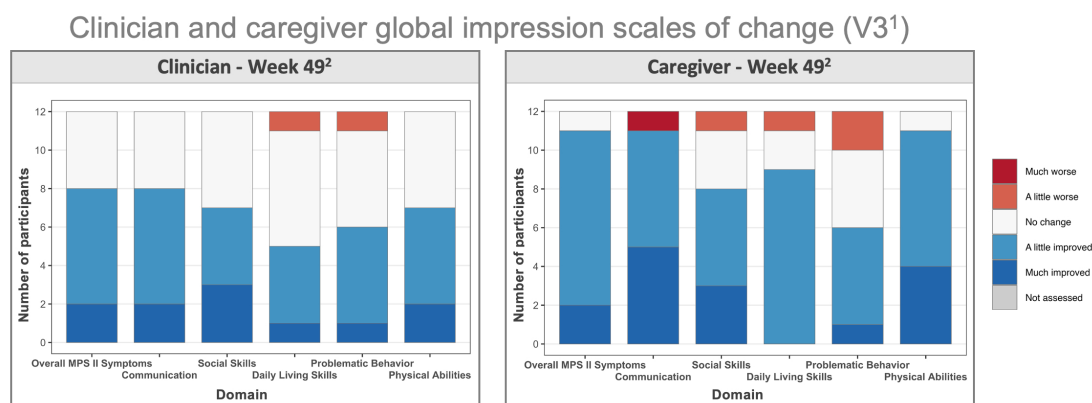
As presented at SSIEM 2022, data from additional participants reaching one year of dosing with DNL310 continued to show rapid normalization of cerebrospinal fluid (“CSF”) heparan sulfate levels to healthy levels (**Figure 5**) as well as improvements in biomarkers of lysosomal function consistent with durable CNS activity. The safety profile of DNL310 with up to 85 weeks of dosing continued to be similar to standard of care. In addition, new longer-term exploratory outcomes data from clinician and caregiver global impression scales of change suggested most participants improve or stabilize at week 49 as compared to baseline of the Phase 1/2 study (**Figure 6**).

We have initiated enrollment in the randomized, controlled Phase 2/3 COMPASS study, which is expected to enroll approximately 54 MPS II patients. Upon completion of the ongoing Phase 1/2 study, and together with data from the global COMPASS study, we expect this combined data package will potentially support registration.



Preliminary normal range (10th and 90th %ile) determined using 30 healthy adult CSF samples (age range 18-81 years, median 52 years). Total CSF GAG levels are similar in adults and children (Hendriksz et al., 2015). Normal range for CSF Heparan Sulfate (ng/mL): (39.1 - 92.51).

Figure 5: CSF heparan Sulfate: Rapid response was observed in most patients after four to six weekly intravenous doses of DNL310. Normal CSF heparan sulfate levels were achieved by week 24 and sustained in all participants who had reached week 49 (89% mean reduction from baseline), including in two children who entered the study with high levels of anti-IDS antibodies.



¹Week 49 CGI/CaGI-C data from the 4 participants assessed with V2 is consistent with the depicted Week 49 CGI/CaGI-C V3 data
²Week 24 data V2 and V3 (n=21) was consistent with the depicted Week 49 data, and Week 24 V2 data (n=15) was presented at WORLD 2022 (Bakardjiev et al.)

Figure 6: Exploratory clinical outcomes data for participants who had assessments at week 49 of the Phase 1/2 study: Most participants demonstrated improvements or stabilization across all domains since entering the study, as reported by clinicians and parents/caregivers. These findings are based on Clinician Global Impression Scales of Change (“CGI-C”) and Caregiver Global Impression Scales of Change (“CaGI-C”), which are standardized assessment scales used to measure change and modified to measure specific domains impacted by Hunter syndrome, including communication, daily living, social skills, physical abilities and problematic behavior.

TAK-594/DNL593 (PTV:PGRN) Program for FTD-GRN

We are collaborating with Takeda to co-develop and co-commercialize TAK-594/DNL593 (PTV:PGRN), an intravenously administered, Protein Transport Vehicle (“PTV”)-enabled recombinant progranulin (PTV:PGRN) protein designed to restore normal levels of progranulin (“PGRN”) in the brain without interfering with normal PGRN transport and processing. Mutations in the granulin (“GRN”) gene, which encodes the PGRN protein, result in reduced levels of PGRN and are amongst the most common genetic causes of frontotemporal dementia (“FTD”). Preclinical proof of concept demonstrates that PTV enhances brain uptake of recombinant PGRN as well as uptake by multiple cell types in the brain, including neurons and microglia, as compared to non-TV PGRN. In addition, TAK-594/DNL593 rescued both neurodegeneration and microglial dysfunction in PGRN-deficient mice. Our improved mechanistic understanding of the role of PGRN in lysosomal function indicates that direct delivery of TAK-594/DNL593 to the brain may be an effective therapeutic approach to increase PGRN levels in lysosomes for the potential treatment of people with certain types of FTD, especially FTD-GRN caused by PGRN deficiency.

Together with Takeda, we initiated a Phase 1/2 clinical trial of TAK-594/DNL593 for FTD-GRN in 2022. Initial results from Part A of this study demonstrate that single ascending doses were generally well tolerated in healthy volunteers and were associated with dose-dependent increases in PGRN levels measured in CSF. The data support enrollment of participants with FTD-GRN in Part B of the study, which is expected to commence in Q4 2022.

TAK-920/DNL919 (ATV:TREM2) Program for Alzheimer's disease

We are collaborating with Takeda to co-develop and co-commercialize TAK-920/DNL919 (ATV:TREM2), an ATV designed to activate TREM2 and improve microglial function. TREM2 is a receptor expressed on microglia, the resident immune cells of the brain. Loss of function TREM2 genetic mutations are strongly associated with an increased risk for AD. Animal model data demonstrate enhanced brain uptake with TAK-920/DNL919 as compared to a non-ATV TREM2 antibody and improved pharmacodynamic response.

Together with Takeda, we initiated a Phase 1 single ascending dose study in healthy volunteers in the Netherlands in 2022 which is actively enrolling participants. In January 2022, we announced that the TAK-920/DNL919 Investigational New Drug (“IND”) application had been placed on clinical hold by the U.S. Food and Drug Administration (“FDA”). We plan to continue to engage with the FDA and regulatory authorities in Europe to define the path forward for the TAK-920/DNL919 clinical program, including plans to advance into a Phase 1b study in patients with AD.

DNL126 (ETV:SGSH) Program for MPS IIIA (Sanfilippo Syndrome A)

DNL126 (ETV:SGSH) is our second most advanced ETV program following DNL310 (ETV:IDS). DNL126 is in development for the potential treatment of MPS IIIA (Sanfilippo syndrome A), a rare lysosomal storage disease that causes fatal brain damage. MPS IIIA is caused by genetic defects that result in a reduction in the lysosomal activity of N-sulfoglucosamine sulfohydrolase (“SGSH”), an enzyme responsible for degrading heparan sulfates in the lysosome. There are no approved treatments for MPS IIIA. Preclinical data demonstrated that DNL126 reduced heparan sulfate in a dose-dependent manner in brain and cerebrospinal fluid in an MPS IIIA model. Submission of an IND application is planned for the first half of 2023.

DNL622 (ETV:IDUA) for MPS I (Hurler syndrome)

Alpha-L-iduronidase (“IDUA”) is an enzyme responsible for degrading heparan and dermatan sulfate in the lysosome. Genetic defects in IDUA result in a reduction or absence of lysosomal IDUA activity and cause Hurler syndrome (or MPS I), which is characterized by alterations in the skeleton, heart, respiratory system, and the brain. DNL622 (ETV:IDUA) is a recombinant IDUA enzyme engineered to cross the BBB, to replace IDUA, and to treat the cognitive, behavioral and physical manifestations of the disease. DNL622 is currently in the IND-enabling stage of preclinical development.

Oligonucleotide Transport Vehicle platform

Oligonucleotides, such as antisense oligonucleotides ("ASOs"), are a novel class of biotherapeutics with the potential to address the root cause of many diseases through modulation of gene expression. This class, however, has been limited in its potential for treatment of neurodegenerative diseases, primarily due to the challenge of delivering effective amounts of drug to relevant brain regions. Direct injection into the cerebrospinal fluid (e.g., intrathecal injection) or certain brain regions has not achieved the robust biodistribution into deep brain tissue, which may be necessary for effective therapeutic activity.

Nonhuman primate data with our OTV demonstrated that intravenous delivery of an ASO enabled by OTV technology resulted in broad brain biodistribution of the ASO (**Figure 7**) and knockdown of target gene expression in all brain cell types, which was superior to intrathecal administration of the ASO. These data support the potential of our OTV platform to enable peripheral administration of oligonucleotide therapeutics and to address a wide range of neurodegenerative diseases (**Figure 8**).

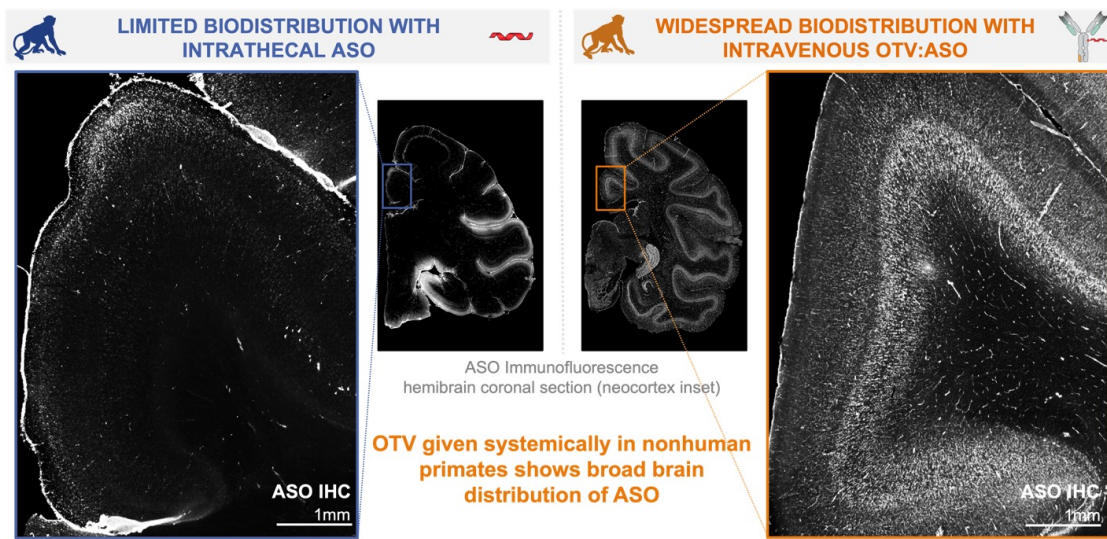


Figure 7: Broad brain biodistribution of ASO enabled by OTV technology after intravenous administration (right) as compared to limited brain biodistribution of ASO delivered intrathecally (left).

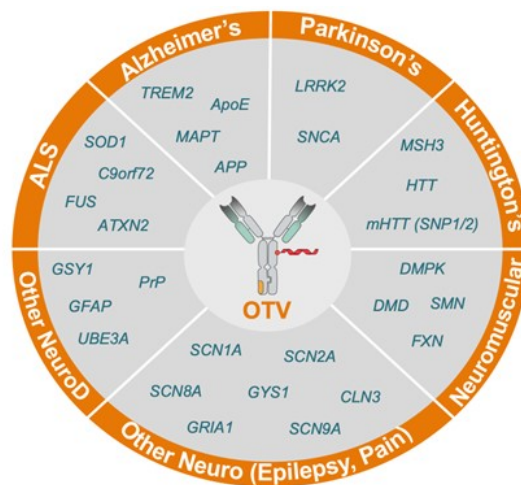


Figure 8: OTV is designed to open a large potential indication space in neurodegeneration and beyond by enabling superior biodistribution of ASOs across brain regions; providing superior knockdown of target gene expression across all cell types; and enabling intravenous dosing of oligonucleotide therapeutics.

Other TV-Enabled Discovery Programs

Our portfolio includes additional preclinical programs, including programs targeting Abeta (“ATV:Abeta”) and HER2 (“ATV:HER2”).

Targeting Abeta plaques in the brain has been investigated by the field as a therapeutic approach to treat AD. Our ATV:Abeta utilizes the TV platform to enable increased brain exposure and target engagement of anti-Abeta. In preclinical studies in mice, we demonstrated a notable difference in ATV:Abeta localization with plaques, and quantification revealed up to a 17-fold increase in ATV:Abeta signal colocalization with plaques compared to a non-TV-enabled Abeta antibody. This significant increase in target engagement compared to the standard antibody could indicate potential for superior efficacy or an improved therapeutic window. Biogen has an exclusive option to license ATV:Abeta, which may be triggered up to initiation of IND-enabling studies.

HER2 is a growth factor receptor that is over-expressed in multiple cancers, including breast, colorectal, and gastric cancer. Up to half of patients diagnosed with metastatic HER2-positive breast cancer have brain metastases for which limited treatment options exist. Using ATV, we have engineered mono- and bispecific formats of HER2 antibodies. In preclinical mouse studies, we have demonstrated improved anti-tumor activity of ATV-enabled HER2 antibodies in a HER2-positive peripheral tumor model. Our bispecific ATV:HER2 antibody demonstrated improved peripheral anti-tumor activity as compared to non-ATV HER2 antibodies as well as enhanced brain uptake as compared to a non-ATV HER2 antibody. The data support the potential for ATV:HER2 to treat HER2-positive peripheral tumors and brain metastases and to further validate the potential for TV applications in oncology.

Our Brain-Penetrant Small Molecule Programs

BIIB122/DNL151 LRRK2 Inhibitor Program for Parkinson's disease

We are collaborating with Biogen to co-develop and co-commercialize our small molecule inhibitors of LRRK2 for PD. Inhibition of LRRK2 may have the ability to restore impaired lysosomal function, which is implicated in PD pathology and disease progression. BIIB122/DNL151 is the most clinically advanced small molecule inhibitor of LRRK2 currently in clinical testing for PD. Results from Phase 1 and Phase 1b trials of BIIB122/DNL151 in healthy volunteers and patients with PD, respectively, showed robust target and pathway engagement as measured by pS935 LRRK2 (**Figure 9**) and pT73 Rab10 (“pRab10”), respectively. In addition, a dose-dependent reduction in urine of the lysosomal lipid 22:6-bis[monoacylglycerol] phosphate (“BMP”), a biomarker of lysosomal function, was achieved with BIIB122/DNL151 treatment, providing evidence supporting improvement of lysosomal function. BIIB122/DNL151 was generally well tolerated across a broad range of doses for up to 28 days, the longest treatment duration in both studies.

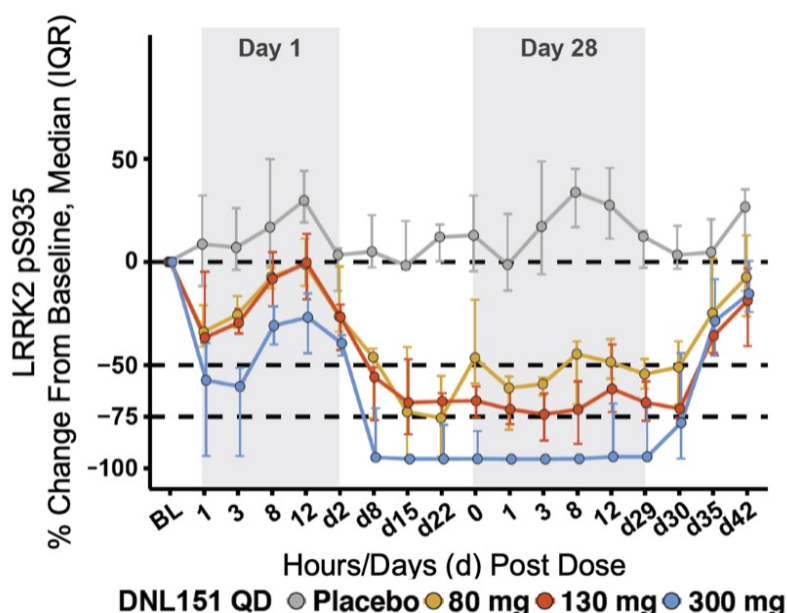


Figure 9: BIIB122 reduces pS935 LRRK2 (whole blood), consistent with reduced LRRK2 activity in Phase 1b trial of participants with PD.

Biogen is conducting two global late-stage clinical trials of BIIB122/DNL151: the Phase 2b LUMA study, which commenced in May 2022 and is evaluating the efficacy and safety of BIIB122/DNL151 as compared to placebo in approximately 640 participants with early-stage PD; and the Phase 3 LIGHTHOUSE study in approximately 400 participants with PD with a confirmed LRRK2 pathogenic variant, which commenced dosing in September 2022.

SAR443820/DNL788 RIPK1 Inhibitor Program for CNS Disease

We are collaborating with Sanofi on the development of small molecules that inhibit RIPK1, a critical signaling protein in the tumor necrosis factor (“TNF”) receptor pathway and a regulator of inflammation and cell death. Increased RIPK1 activity in the brain drives neuroinflammation and cell necroptosis and contributes to neurodegeneration. RIPK1 inhibition has been shown to have beneficial effects in preclinical models of ALS, multiple sclerosis (“MS”), AD, and other diseases.

SAR443820/DNL788 is our lead CNS-penetrant RIPK1 inhibitor in clinical development. Sanofi completed a Phase 1 trial of SAR443820/DNL788 in healthy volunteers in which robust target engagement was demonstrated at doses that were generally well tolerated. In 2022, Sanofi commenced dosing in the HIMALAYA global Phase 2 study of SAR443820/DNL788 and expects to enroll approximately 260 participants with ALS. A Phase 2 study of SAR443820/DNL788 in MS is also planned. In addition, we are leading preclinical exploration of SAR443820/DNL788 as a potential treatment for AD.

DNL343 eIF2B Program for ALS

We are developing DNL343 as a novel eIF2B activator with first-in-class potential for the treatment of ALS and other indications. DNL343 is designed to inhibit the cellular integrated stress response (“ISR”) to prevent or slow disease progression that is associated with stress granule formation and TDP-43 aggregation, a hallmark pathology present in nearly all individuals with ALS. Results from a Phase 1 study in healthy volunteers demonstrated that DNL343 was generally well tolerated for up to 14 days of dosing, with robust distribution in the CNS. Furthermore, biomarker assessments of DNL343 treatment confirmed ISR pathway engagement, demonstrating modulation of ISR-dependent genes and proteins in a dose-dependent manner (**Figure 10**).

We are conducting a Phase 1b multicenter, randomized, placebo-controlled, double-blind, 28-day trial followed by an 18-month open-label extension, designed to evaluate the safety, pharmacokinetics and pharmacodynamics of DNL343 in approximately 30 participants with ALS. Dosing in this study began in the third quarter of 2021 and we expect that safety and biomarker results will be available later in 2022. Based on the Phase 1 data and review of blinded data from the ongoing Phase 1b study, we have initiated planning for late-stage development of DNL343 in ALS. We expect to initiate a late-stage study of DNL343 in ALS in 2023.

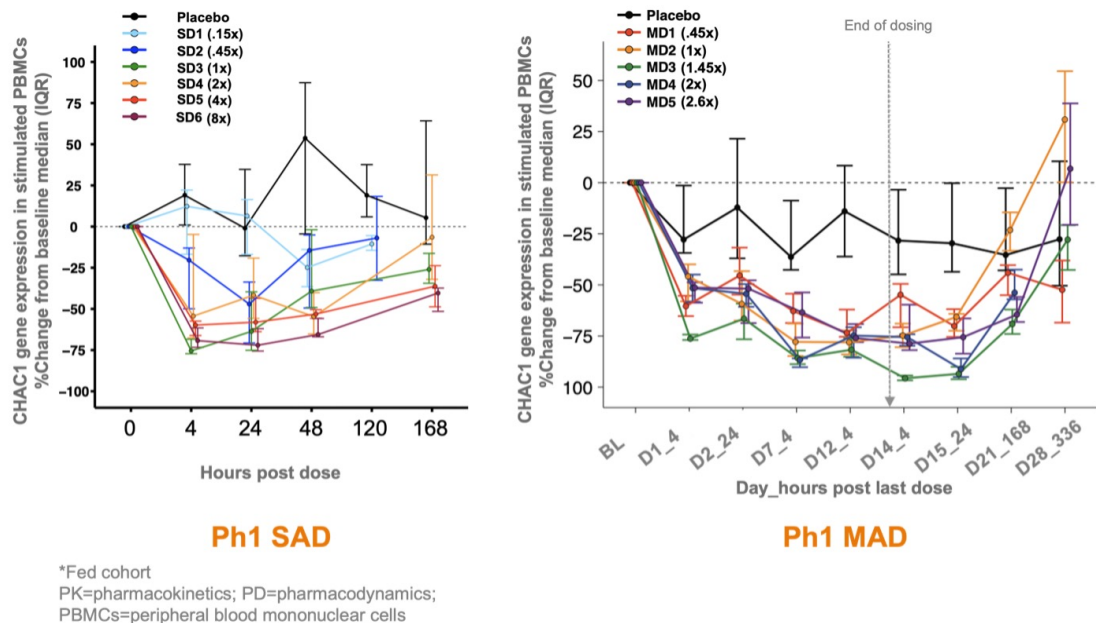


Figure 10: DNL343 inhibits ISR-dependent gene expression of CHAC1 in blood samples from healthy volunteers after single- and multiple-ascending doses (left and right panels, respectively).

Other Programs

SAR443122/DNL758 RIPK1 Inhibitor Program for Peripheral Inflammatory Diseases

Our collaboration with Sanofi also includes the peripherally-restricted RIPK1 inhibitor SAR443122/DNL758 which is currently being evaluated in a Phase 2 trial in patients with cutaneous lupus erythematosus (“CLE”). Sanofi also plans to initiate a Phase 2 trial of SAR443122/DNL758 in patients with ulcerative colitis.

Recent Developments

As of September 30, 2022, we estimate we had approximately \$1.11 billion in cash, cash equivalents and marketable securities. This financial data as of September 30, 2022 is preliminary and is based on information available to management as of the date of this prospectus supplement and is subject to completion by management of our unaudited condensed consolidated financial statements as of and for the nine-months ended September 30, 2022. Our independent registered public accountants have not audited, reviewed or performed any procedures with respect to such preliminary financial data and accordingly do not express an opinion or any other form of assurance with respect thereto. These results could change as a result of further review. Complete quarterly results will be included in our Quarterly Report on Form 10-Q for the quarter ended September 30, 2022.

Company Information

We were incorporated in Delaware in October 2013. Our principal executive offices are located at 161 Oyster Point Blvd, South San Francisco, CA and our telephone number at that address is (650) 866-8548. We maintain an Internet website at the following address: www.denalitherapeutics.com. The information on, or that can be accessed through, our website does not constitute part of this prospectus supplement or the accompanying prospectus, and you should not rely on any such information in making the decision whether to purchase our common stock.

THE OFFERING

Common stock offered by us	shares. We have also granted the underwriters a 30-day option to purchase up to additional shares.
Common stock to be outstanding following the offering	shares (or shares if the underwriters exercise their option to purchase additional shares in full).
Use of proceeds	<p>We estimate that the net proceeds from this offering will be approximately (or approximately if the underwriters exercise their option to purchase additional shares in full).</p> <p>We intend to use the net proceeds from this offering to fund the following: progression of multiple clinical programs into late-stage trials, including DNL310 (ETV:IDS), DNL343 (eIF2B activator), BIIB122/DNL151 (LRRK2 inhibitor) and SAR443820/DNL788 (RIPK1 inhibitor); potential acceleration of commercial launch readiness in the U.S. and other key global markets; expansion of the TV platform, including development of the OTV platform that will enable broad distribution of ASOs throughout the brain; continued development and expansion of the early-stage portfolio, including advancing three additional NMEs into the clinic; build-out and expansion of in-house clinical manufacturing capabilities for biologic therapeutics, including the manufacture of materials for toxicology studies and drug substance for early human clinical studies; general and administrative expenses, potential future development programs, early-stage research and development, capital expenditures and working capital and other general corporate purposes.</p>
Nasdaq Global Select Market symbol	DNLI
Risk factors	Investing in our securities involves risks. See "Risk Factors" beginning on page S-21 of this prospectus supplement and other information included or incorporated by reference into this prospectus supplement and the accompanying prospectus for a discussion of the factors you should carefully consider before deciding to invest in our securities.

The number of shares of our common stock to be outstanding after the offering is based on 123,157,278 shares of common stock outstanding as of June 30, 2022, and excludes:

- 15,158,522 shares of common stock issuable upon the exercise of stock options outstanding as of June 30, 2022, at a weighted average exercise price of \$26.96 per share;
- 2,898,742 shares of common stock issuable upon the vesting of restricted stock units outstanding as of June 30, 2022;
- up to an aggregate of \$400.0 million of shares of common stock that may be sold under our "at-the-market" program with Goldman Sachs & Co. LLC, SVB Securities LLC and Cantor Fitzgerald & Co.;

- 10,636,762 shares of common stock reserved for future issuance under our 2017 Equity Incentive Plan, or the 2017 Plan, as of June 30, 2022, plus any future increases in the number of shares of common stock reserved for issuance under the 2017 Plan pursuant to the evergreen provision of the 2017 Plan; and
- 4,568,809 shares of common stock reserved for future issuance under our 2017 Employee Stock Purchase Plan, or the 2017 ESPP, as of June 30, 2022, plus any future increases in the number of shares of common stock reserved for issuance under the 2017 ESPP pursuant to the evergreen provision of the 2017 ESPP.

Except as otherwise indicated, all information in this prospectus supplement assumes:

- no exercise by the underwriters of their option to purchase up to additional shares of common stock in this offering; and
- no exercise or settlement of stock options, RSUs or other equity awards described above, no grant of additional awards under our 2017 Plan, and no issuance of shares under the 2017 ESPP, in each case, after June 30, 2022.

RISK FACTORS

Investing in our securities involves a high degree of risk. In addition to the other information contained in this prospectus supplement, the accompanying prospectus and in the documents we incorporate by reference, you should carefully consider the risks discussed below, before making a decision about investing in our securities. The risks and uncertainties discussed below are not the only ones facing us. Additional risks and uncertainties not presently known to us, or that we currently see as immaterial, may also harm our business. If any of these risks occur, our business, financial condition and operating results could be harmed, the trading price of our common stock could decline and you could lose part or all of your investment.

Risks Related to Our Business, Financial Condition and Capital Requirements

We are in the clinical stages of drug development and have a 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 a clinical-stage biopharmaceutical company with a limited operating history, focused on developing therapeutics for neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and 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. Our clinical stage programs, ATV:TREM2, PTV:PGRN, eIF2B, RIPK1, ETV:IDS and LRRK2, are in various phases ranging from Phase 1 through Phase 3. We have not initiated clinical trials for any of our other current product candidates. To date, we have not 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 limited 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 clinical-stage biopharmaceutical companies in rapidly evolving fields, and we have not yet demonstrated an ability to successfully overcome such risks and difficulties. If we do not address these risks and difficulties successfully, our business will suffer.

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

We have incurred significant net losses since our inception, including net losses of \$58.8 million and \$124.0 million for the three and six months ended June 30, 2022, respectively. As of June 30, 2022, we had an accumulated deficit of \$769.0 million.

We have invested significant financial resources in research and development activities, including for our preclinical and clinical product candidates and our TV platform. 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 and incur increased stock-based compensation, especially in light of a competitive compensation environment;
- provide additional internal infrastructure to support our continued research and development operations and any planned commercialization efforts in the future;
- implement additional internal systems and infrastructure related to cybersecurity;
- experience any delays or encounter other issues related to our operations;
- meet the requirements and demands of being a public company;
- defend against any product liability claims or other lawsuits related to our products; and
- build clinical manufacturing capabilities and capacity.

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 TV platform, 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;
- receiving milestone and other payments under our current and any future collaboration arrangements;
- maintaining, protecting, expanding and enforcing our portfolio of intellectual property rights, including patents, trade secrets and know-how;
- attracting, hiring and retaining qualified personnel and the impact of the increased labor market competition;
- general economic conditions, including conditions resulting from rising inflation and interest rates, geopolitical uncertainty and instability or war; and
- addressing any delays in our clinical trials or other impacts resulting from the ongoing COVID-19 pandemic.

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 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 current or 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. We currently fund our operations primarily with the proceeds from our follow-on offering completed in January 2020, and payments received from our collaboration agreements with Biogen, Sanofi and Takeda. We have a diversified portfolio with numerous programs at various preclinical and clinical stages of development. Developing our product candidates is expensive, and we expect to continue to spend substantial amounts as we fund our early-stage research projects, and continue to advance our programs through preclinical and clinical development. Even if we are successful in developing our product candidates, obtaining regulatory approvals and launching and commercializing any product candidate will require substantial additional funding.

As of September 30, 2022, we estimate we had approximately \$1.11 billion in cash, cash equivalents and marketable securities. Our independent registered public accountants have not audited, reviewed, or performed any procedures with respect to such preliminary financial data and accordingly do not express an opinion or any other form of assurance with respect hereto. 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. Changing circumstances, some of which may be beyond our control, such as geopolitical uncertainty, rising inflation or interest rates or a perceived or actual economic downturn, may cause us to increase our spending significantly faster than we currently anticipate, and we may need to seek additional funds sooner than planned. We may also need to raise additional funds sooner than we anticipate if we choose to expand more rapidly than we presently anticipate.

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

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

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

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

A pandemic, epidemic or outbreak of an infectious disease, such as COVID-19, or the perception of its effects, may materially and adversely affect our business, operations and financial condition.

Public health outbreaks, such as epidemics or pandemics involving infectious or contagious diseases, such as COVID-19, may significantly disrupt our business. Such outbreaks pose the risk that we or our employees, contractors, suppliers, and other partners may be prevented from conducting business activities for an indefinite period of time due to the spread of the disease, due to shutdowns that may be requested or mandated by federal, state and local governmental authorities or certain employers, or due to the economic consequences associated with the pandemic. Business disruptions could include disruptions or restrictions on our ability to travel, as well as temporary closures of our facilities and the facilities of our partners, clinical trial sites, service providers, suppliers or contract manufacturers. For example, the COVID-19 pandemic caused a temporary disruption in our ability to recruit participants for our clinical trials in the calendar year 2020 and the first quarter of 2021. While it is not possible at this time to predict whether another pandemic, epidemic or infectious disease outbreak similar to COVID-19 will materialize, any measures taken by the governments of countries and local authorities in response to such future health crises have the potential to disrupt and delay the initiation of new clinical trials, the progress of our ongoing clinical trials, and could disrupt and delay our preclinical activities, and potentially the manufacture or shipment of both drug substance and finished drug product of our product candidates for preclinical testing and clinical trials and adversely impact our business, financial condition or operating results.

The continued impact of the COVID-19 pandemic may materially and adversely affect our business, operations and financial condition.

We are actively monitoring, evaluating and responding to developments relating to COVID-19, including new strains of the disease that have emerged, vaccination status both locally and globally, and other COVID-19 related protocols and travel restrictions as set forth by the CDC and other state, local and government authorities. In response to the COVID-19 pandemic in 2020, we implemented policies that enabled some of our employees to work remotely, and such policies may continue for an indefinite period. We also implemented various safety protocols for all on-site personnel, including COVID-19 testing procedures and compliance measures for social distancing and use of personal protective equipment and continue to maintain appropriate protocols in accordance with federal, state and local regulation. Our priority is to protect the health and safety of our employees, community, partners and clinical trial participants, while working to ensure the sustainability of our business operations.

Although restrictions related to the COVID-19 pandemic were lifted in many of our locations for a period of time, new resurgences could occur at any time, which may cause disruptions to our business going forward. Examples of disruptions to our business from COVID-19 have included:

- delays or difficulties in enrolling patients in our clinical trials, particularly elderly subjects, who are at a higher risk of complications from COVID-19;
- difficulties interpreting data from our clinical trials due to the possible effects of COVID-19 on subjects enrolled in our clinical trials that contract COVID-19;
- delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff;
- diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of clinical trials;
- interruption of key clinical trial activities, such as clinical trial site monitoring, due to limitations on travel imposed or recommended by federal or state governments, employers and others;
- delays in receiving approval from local regulatory authorities to initiate our planned clinical trials;
- interruption of, or delays in receiving, supplies of our product candidates from our contract manufacturing organizations due to staffing shortages, production slowdowns or stoppages;
- delays or difficulties in furthering our preclinical and clinical programs, due to interruptions or limitations in our third party service providers' business operations;
- interruption in global shipping that may affect the transport of clinical trial materials, such as investigational drug products used in our clinical trials;
- changes in clinical trial site procedures and requirements as well as regulatory requirements for conducting clinical trials during the COVID-19 pandemic;
- delays or interruptions in the operations of or necessary interactions with the FDA or other regulators; and
- limitations on employee resources that would otherwise be focused on the conduct of our nonclinical studies and clinical trials, either because of sickness of employees and their families or the desire of employees to avoid contact with large groups of people.

Our business is headquartered in California, which was more severely affected by the COVID-19 pandemic than some other parts of the country. In June 2021, certain pandemic-related restrictions were lifted in California; however, should COVID-19 cases significantly increase, the relevant counties or state may re-institute pandemic-related restrictions. Our primary operations are located in South San Francisco and many of our employees have chosen to telecommute. Due to telecommuting patterns, modified schedules and work protocols to enable adequate physical distancing, our laboratory operations have at times and may again operate with decreased efficiency, which may impact certain of our operations over the near term and long term. Should these developments continue or worsen, our operations and program timelines may be negatively impacted and could result in the incurrence of additional costs.

We have clinical trial sites for our clinical studies in the United States and Europe, any of which may be affected by subsequent variants of the coronavirus, and the availability of vaccines at the clinical trial site locations. If healthcare facilities and offices are required to focus limited resources on non-clinical trial matters such as treatment of COVID-19 patients, then patient screening, new patient enrollment, and monitoring and data collection could be affected. For example, in 2020, we experienced a pause in enrollment in our BIIB122/DNL151 Phase 1 and Phase 1b trials, our DNL343 Phase 1 trial, and our ETV:IDS program observational biomarker study. In all cases, recruitment resumed within several months; however, we have subsequently experienced certain delays in patient enrollment, and further pauses or delays could occur in our clinical trials, including as a result of social or economic unrest caused by the ongoing COVID-19 pandemic.

In March 2020, the FDA issued guidance, which the FDA subsequently updated, on conducting clinical trials during the pandemic, which describes a number of considerations for sponsors of clinical trials impacted by the pandemic, including the requirement to include in the clinical trial report contingency measures implemented to manage the trial and any disruption of the trial as a result of the COVID-19 pandemic, among others. In June 2020, the FDA issued guidance on manufacturing practice considerations for responding to COVID-19 infection in employees in drug and biologic products manufacturing, including recommendations for manufacturing controls to prevent contamination of the products. Other COVID-19 related industry guidance documents published by the FDA include updates to previous guidance related to Good Manufacturing Practices, guidance on remote interactive evaluations of drug manufacturing and bioresearch monitoring facilities, and guidance on drug product manufacturing and supply chain inspections, among others. Should the FDA issue additional guidance with respect to COVID-19 protocols as relates to the implementation of our clinical trials, the costs of such clinical trials may increase. Further, we may be required to develop and implement additional clinical trial policies and procedures designed to help protect subjects from the COVID-19 virus, and any variants of the coronavirus that may emerge in the future. The extent to which the COVID-19 pandemic impacts our business, preclinical studies and clinical trials will depend on future developments, which are highly uncertain and cannot be predicted.

To the extent the COVID-19 pandemic continues to adversely affect our business, operations and financial condition, it may also have the effect of heightening many of the risks described in this "Risk Factors" section.

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

Research and development of biopharmaceutical products is inherently risky. We are heavily dependent on the successful development of our BBB platform technology and the programs currently in our pipeline, which are in the preclinical and clinical development stages. 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 many 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 clinical trials, and providing general and administrative support for these operations. Our future success is dependent on our ability to successfully develop, obtain regulatory approval for, and then successfully commercialize our product candidates, and we may fail to do so for many reasons, including the following:

- our product candidates may not successfully complete preclinical studies or clinical trials;
- our drug delivery platform technology designed to deliver large molecule therapeutics across the BBB may not be clinically viable;

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

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

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

We have never completed a clinical development program. We have previously discontinued the development of certain molecules prior to completion of preclinical development because we did not believe they met our criteria for potential clinical success. Further, we cannot be certain that any of our product candidates will be successful in clinical trials. For instance, in June 2020, together with our collaboration partner Sanofi, we paused clinical activities with DNL747 to accelerate development of SAR443820/DNL788, in part due to DNL747 preclinical chronic toxicity studies. We may in the future advance product candidates into clinical trials and terminate such trials prior to their completion.

If any of our product candidates successfully complete clinical trials, we generally plan to seek regulatory approval to market our product candidates in the United States, the European Union ("EU"), and in additional foreign countries where we believe there is a viable commercial opportunity. We have never commenced, compiled or submitted an application seeking regulatory approval to market any product candidate. We may never receive regulatory approval to market any product candidates even if such product candidates successfully complete clinical trials, which would adversely affect our viability. To obtain regulatory approval in countries outside the United States, we must comply with numerous and varying regulatory requirements of such other countries regarding safety, efficacy or potency, purity, 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 potency, 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 ("IND"), or a clinical trial application ("CTA"), will result in the FDA or European Medicines Agency ("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 trial 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 ("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 trial 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 approval policies or regulations of the FDA or comparable foreign regulatory authorities;
- changes in the standard of care on which a clinical development plan was based, which may require new or additional trials;
- the cost of clinical trials of our product candidates being greater than we anticipate;
- clinical trials of our product candidates producing negative or inconclusive results, which may result in our deciding, or regulators requiring us, to conduct additional clinical trials or abandon product development programs;
- transfer of manufacturing processes from our academic collaborators to larger-scale facilities operated by a CDMO or by us, and delays or failure by our CDMOs or us to make any necessary changes to such manufacturing process;
- 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; and
- delays associated with the ongoing COVID-19 pandemic.

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.

For example, in January 2022, we announced that the TAK-920/DNL919 (ATV:TREM2) IND application had been placed on clinical hold by the FDA. While we initiated a Phase 1 study in the Netherlands, we plan to continue to engage with the FDA and European regulatory authorities to define the path forward for the TAK-920/DNL919 clinical program.

Refer to “Item 1. Business—Our Programs” in our Annual Report on Form 10-K for the year ended December 31, 2021 and incorporated herein by reference for a more detailed discussion of adverse effects (“AEs”) and significant adverse effects (“SAEs”) observed in our reported clinical trials for BIIB122/DNL151 and DNL310.

We cannot assure you that the IND clinical hold on TAK-920/DNL919 will be lifted, or that BIIB122/DNL151, DNL310, DNL343, SAR443820/DNL788, SAR443122/DNL758, and TAK-594/DNL593 or our other product candidates will not be subject to new, partial or full clinical holds in the future which may impact development plans.

We may in the future advance product candidates into clinical trials and terminate such trials prior to their completion, which could adversely affect our business. Further, after the commencement of clinical trials, we may pause the advancement of lead molecules in favor of a backup molecule with a superior safety or efficacy profile, such as we did in our RIPK1 program, switching our focus from DNL747 to SAR443820/DNL788.

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 and/or retaining 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 and retention in our clinical trials for a variety of reasons, including:

- inability or delay in enrollment of patients due to a variety of reasons, including outbreaks and public health crises, such as the ongoing COVID-19 pandemic;
- 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, including the risk of higher drop-out rates if participants become infected with the COVID-19 virus or other infectious diseases that impact their participation in our trials.

Our inability to enroll and retain a sufficient number of patients for our clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for our product candidates and jeopardize our ability to obtain marketing approval for the sale of our product candidates. Furthermore, even if we are able to enroll a sufficient number of patients for our clinical trials, we may have difficulty maintaining participation in our clinical trials through the treatment and any follow-up periods, which could delay or negatively impact the anticipated readouts from our clinical trials, delay our regulatory submissions, and increase the costs of the clinical trials.

Our clinical trials may reveal significant adverse events, toxicities, or other side effects and may fail to demonstrate substantial evidence of the safety and efficacy or potency 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 or potency 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 or potency 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 potency 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, or that the product candidates will be approved for the currently proposed indications, 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, such as requiring us to narrow our indications to a smaller subset of the patient population, may limit the scope and use of our product candidate, which may also limit its commercial potential.

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

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

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

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

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

There are a number of large pharmaceutical and biotechnology companies that are currently pursuing the development of products for the treatment of the neurodegenerative disease indications for which we have research programs, including Alzheimer's disease, Parkinson's disease, Hunter syndrome, and ALS. Companies that we are aware are developing therapeutics in the neurodegenerative disease area include companies with significant financial resources, such as AbbVie, Alector, AstraZeneca, Biogen, Bristol-Myers Squibb, Eli Lilly (including Prevail Therapeutics, its wholly owned subsidiary), E-Scape Bio, GlaxoSmithKline, Ionis, JCR Pharmaceuticals, Johnson & Johnson, Novartis, Roche (including Genentech, its wholly owned subsidiary), 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 and capabilities, which we are actively building. We recently entered into an operating lease for approximately 78,000 square feet of laboratory, office and warehouse premises in Salt Lake City, Utah and have initiated the build-out of our Utah site to expand our clinical manufacturing capabilities for biologic therapeutics including the manufacture of materials for toxicology studies and drug substance for early human clinical studies. In addition, building internal manufacturing capacity carries 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, and our current and future efforts to scale our internal manufacturing capabilities may not succeed.

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

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

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

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

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

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

- unforeseen costs and expenses associated with creating an independent commercialization organization.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Risks Related to Regulatory Approval and Other Legal Compliance Matters

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

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

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

- the FDA, EMA or comparable foreign regulatory authorities may disagree with the design, implementation or results of our clinical trials;
- the FDA, EMA or comparable foreign regulatory authorities may determine that our product candidates are not safe and effective, only moderately effective or have undesirable or unintended side effects, toxicities or other characteristics that preclude our obtaining marketing approval or prevent or limit commercial use;
- the population studied in the clinical program may not be sufficiently broad or representative to assure efficacy or potency 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, BIIB122/DNL151, DNL310, SAR443820/DNL788, SAR443122/DNL758, DNL343, TAK-594/DNL593 and TAK-920/DNL919 are currently our only clinical stage product candidates. In our completed Phase 1b clinical trial of former product candidate DNL201 in patients with Parkinson's disease, there was one SAE considered unrelated to the drug, and at the high dose, there was one severe AE (headache) leading to dose reduction and one study withdrawal (headache and nausea). Adverse events and other side effects may result from higher dosing, repeated dosing and/or longer-term exposure to our product candidates and could lead to delays and/or termination of the development of these product candidates.

On January 13, 2022, we announced that the TAK-290/DNL919 (ATV:TREM2) IND application had been placed on clinical hold by the FDA. We received a formal clinical hold letter which included the FDA's observations related to the preclinical toxicology assessment and to provide the information requested to initiate clinical studies, including proposed changes to the clinical trial protocol, the informed consent form, and the investigator brochure. We plan to continue to engage with regulatory authorities in the U.S. and Europe to define the path forward for the TAK-920/DNL919 clinical program.

In 2020, we paused clinical studies with DNL747 in our RIPK1 program. Chronic toxicity studies with DNL747 in cynomolgus monkeys showed dose- and duration-dependent adverse preclinical findings at exposures higher than those tested in the clinic. These findings, which are considered off-target and molecule-specific, may impact the ability to increase the dose of DNL747 and achieve higher levels of target inhibition without time consuming additional clinical safety studies in patients to evaluate the long-term safety and tolerability.

Drug-related side effects could affect patient recruitment, the ability of enrolled patients to complete the trial, 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 cannot predict whether our product candidates will cause toxicities in humans that would preclude or lead to the revocation of regulatory approval based on nonclinical studies or early-stage clinical trials.

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

We currently conduct one or more of our clinical trials outside the United States, including in Europe, and may continue to do so in the future. The acceptance of 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, and 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 or potency, and other post-market information, including both federal and state requirements in the United States and requirements of comparable foreign regulatory authorities.

While healthcare professionals are free to use and prescribe drug products for off-label uses, FDA strictly regulates manufacturers' promotional claims of drug products. In particular, a product may not be promoted for uses that are not approved by the FDA as reflected in the FDA-approved labeling. The FDA, the Department of Justice, the Inspector General of the Department of Health and Human Services, among other government 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, including large civil and criminal fines, penalties, and enforcement actions. If we cannot successfully manage the promotion of our approved product candidates, we could become subject to significant liability, which would materially adversely affect our business and financial condition.

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

Any regulatory approvals that we receive for our product candidates will be subject to limitations on the approved indicated uses for which the product may be marketed and promoted or to the conditions of approval (including the requirement to implement a Risk Evaluation and Mitigation Strategy) or contain requirements for potentially costly post-marketing testing. We will be required to report certain adverse reactions and production problems, if any, to the FDA, EMA and comparable foreign regulatory authorities. Any new legislation addressing drug safety issues could result in delays in product development or commercialization, or increased costs to assure compliance. The FDA and other agencies, including the Department of Justice, closely regulate and monitor the post-approval marketing and promotion of products to ensure that they are manufactured, marketed and distributed only for the approved indications and in accordance with the provisions of the approved labeling. We will have to comply with requirements concerning advertising and promotion for our products. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved label. As such, we may not promote our products for indications or uses for which they do not have approval. The holder of an approved NDA, BLA, or MAA must submit new or supplemental applications and obtain approval for certain changes to the approved product, product labeling, or manufacturing process. We could also be asked to conduct post-marketing clinical trials to verify the safety and efficacy of our non-biologic products or safety, purity, and potency for our biologic 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 have received orphan drug designation from the FDA for DNL310, and plan to seek orphan drug designation for additional product candidates, but we may be unable to obtain such designations or to maintain the benefits associated with orphan drug status, including market exclusivity, which may cause our revenue, if any, to be reduced.

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biologic intended to treat a rare disease or condition, defined as a disease or condition with a patient population of fewer than 200,000 in the United States, or a patient population greater than 200,000 in the United States when there is no reasonable expectation that the cost of developing and making available the drug or biologic in the United States will be recovered from sales in the United States for that drug or biologic. Orphan drug designation must be requested before submitting an NDA or BLA. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages, and user-fee waivers. After the FDA grants orphan drug designation, the generic identity of the drug and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. In February 2019, the FDA granted orphan drug designation for our DNL310 program in Hunter syndrome. We plan to seek orphan drug designations for some other product candidates, but we may be unable to obtain such designations.

If a product that has orphan drug designation subsequently receives the first FDA approval for a particular active ingredient for the disease for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other NDA or BLA applications to market the same drug or biologic for the same indication for seven years, except in limited circumstances such as a showing of clinical superiority to the product with orphan exclusivity or if FDA finds that the holder of the orphan exclusivity has not shown that it can assure the availability of sufficient quantities of the orphan product to meet the needs of patients with the disease or condition for which the drug was designated. As a result, even though DNL310 has been granted orphan drug designation and even if one of our product candidates receives orphan exclusivity, the FDA can still approve other drugs that have a different active ingredient for use in treating the same indication or disease. Furthermore, the FDA can waive orphan exclusivity if we are unable to manufacture sufficient supply of our product.

We have received Fast Track designation from the FDA for SAR443820/DNL788 and may seek Fast Track designation from the FDA for additional product candidates. Even if one or more of our product candidates receives Fast Track designation, we may be unable to obtain or maintain the benefits associated with the Fast Track designation.

The FDA has granted Fast Track designation to SAR443820/DNL788. Fast Track designation is designed to facilitate the development and expedite the review of therapies to treat serious conditions and fill an unmet medical need. Programs with Fast Track designation may benefit from early and frequent communications with the FDA, potential priority review and the ability to submit a rolling application for regulatory review. Fast Track designation applies to both the product candidate and the specific indication for which it is being studied. However, if we do not continue to meet the criteria of the Fast Track designation, or if our clinical trials are delayed, suspended or terminated, or put on clinical hold due to unexpected adverse events or issues with clinical supply, we will not receive the benefits associated with the Fast Track program. Furthermore, Fast Track designation does not change the standards for approval. Fast Track designation alone does not guarantee qualification for the FDA's priority review procedures. Fast track designation also does not guarantee our product candidate will be approved in a timely manner, if at all.

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

We may face difficulties from changes to current regulations and future legislation. Current and future legislation may increase the difficulty and cost for us to commercialize our drugs, if approved, and affect the prices we may obtain, including changes in coverage and reimbursement policies in certain market segments for our product candidates, which could make it difficult for us to sell our product candidates, if approved, profitably. Third-party payors, whether domestic or foreign, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In both the United States and certain foreign jurisdictions, there have been a number of legislative and regulatory changes to the health care system that could impact our ability to sell our products profitably. In particular, in 2010, the Affordable Care Act ("ACA"), was enacted, which, among other things, subjected biologic products to potential competition by lower-cost biosimilars, addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program, extended the Medicaid Drug Rebate Program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations, subjected manufacturers to new annual fees and taxes for certain branded prescription drugs, and provided incentives to programs that increase the federal government's comparative effectiveness research. Under the American Rescue Plan Act of 2021, effective January 1, 2024, the statutory cap on Medicaid Drug Rebate Program rebates that manufacturers pay to state Medicaid programs will be eliminated. Elimination of this cap may require pharmaceutical manufacturers to pay more in rebates than it receives on the sale of products, which could have a material impact on our business. In July 2021, the Biden administration released an executive order, "Promoting Competition in the American Economy," with multiple provisions aimed at increasing competition for prescription drugs. In response to this executive order, the Department of Health and Human Services ("HHS") has released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and potential legislative policies that Congress could pursue to advance these principles. In August 2022, Congress passed the Inflation Reduction Act of 2022, which includes prescription drug provisions that have significant implications for the pharmaceutical industry and Medicare beneficiaries, including allowing the federal government to negotiate a maximum fair price for certain high-priced single source Medicare drugs, imposing penalties and excise tax for manufacturers that fail to comply with the drug price negotiation requirements, requiring inflation rebates for all Medicare Part B and Part D drugs, with limited exceptions, if their drug prices increase faster than inflation, and redesigning Medicare Part D to reduce out-of-pocket prescription drug costs for beneficiaries, among other changes. At the state level, a number of states are considering or have recently enacted state drug price transparency and reporting laws that could substantially increase our compliance burdens and expose us to greater liability under such state laws once we begin commercialization after obtaining regulatory approval for any of our products.

Since its enactment, there have been executive, judicial and Congressional challenges to certain aspects of the ACA. In June 2021, the United States Supreme Court held that Texas and other challengers had no legal standing to challenge the ACA, dismissing the case without specifically ruling on the constitutionality of the ACA. Accordingly, the ACA remains in effect in its current form. It is unclear how this Supreme Court decision, future litigation, or healthcare measures promulgated by the Biden administration will impact our business, financial condition and results of operations. Complying with any new legislation or changes in healthcare regulation could be time-intensive and expensive, resulting in material adverse effect 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 2031, with the exception of a temporary suspension implemented under various COVID-19 relief legislation from May 1, 2020 through June 30, 2022, unless additional Congressional action is taken. Under the current legislation, the actual reduction in Medicare payments will vary from 1% in 2022 to up to 4% in the final fiscal year of this sequester. 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. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements.

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. The intent standard under the federal Anti-Kickback Statute was amended by the ACA to eliminate the need to prove specific intent and actual knowledge to establish an Anti-Kickback Statute 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, including the False Claims Act, which can be enforced through civil “qui tam” or “whistleblower” actions, and civil monetary penalty laws generally prohibit individuals or entities, among other things, from knowingly presenting, or causing to be presented, claims for payment or approval from Medicare, Medicaid, or other third-party payors that are false or fraudulent or knowingly making a false statement to improperly avoid, decrease or conceal an obligation to pay money to the federal government. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of these statutes or specific intent to violate them in order to have committed a violation;
- the federal Health Insurance Portability and Accountability Act of 1996 ("HIPAA"), which created new federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 ("HITECH"), and their respective implementing regulations, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information without appropriate authorization;
- the federal Physician Payment Sunshine Act, created under the ACA, and its implementing regulations, which require manufacturers of drugs, devices, biologicals and medical supplies for which payment is available under Medicare, Medicaid or the Children’s Health Insurance Program to report annually to the U.S. Department of Health and Human Services under the Open Payments Program, information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), certain non-physician healthcare professionals (such as physician assistants and nurse practitioners, among others), and teaching hospitals, as well as information regarding ownership and investment interests held by physicians and their immediate family members;
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers; and
- analogous state and foreign laws and regulations, such as state and foreign anti-kickback, false claims, consumer protection and unfair competition laws which may apply to pharmaceutical business practices, including but not limited to, research, distribution, sales and marketing arrangements as well as submitting claims involving healthcare items or services reimbursed by any third-party payer, including commercial insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry’s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government that otherwise restricts payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to file reports with states regarding pricing and marketing information, such as the tracking and reporting of gifts, compensations and other remuneration and items of value provided to healthcare professionals and entities; and state and foreign laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

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

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

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

A wide variety of provincial, state, national, and international laws, and regulations apply to the collection, use, retention, protection, disclosure, transfer and other processing of personal data. These data protection and privacy-related laws and regulations are evolving and may result in ever-increasing regulatory and public scrutiny and escalating levels of enforcement and sanctions. For example, the collection and use of personal data in the EU are governed by the EU General Data Protection Regulation ("GDPR"), which became fully effective on May 25, 2018. The GDPR imposes stringent data protection requirements, including, for example, more robust disclosures to individuals and a strengthened individual data rights regime, shortened timelines for data breach notifications, limitations on retention of information, increased requirements pertaining to special categories of data, such as health data, and additional obligations when we contract with third-party processors in connection with the processing of the personal data. The GDPR also imposes strict rules on the transfer of personal data out of the EU to the United States and other third countries and in the context of clinical trials, we currently rely on patient informed consent as the legal basis for such transfers. In addition, the GDPR provides that EU member states may make their own further laws and regulations limiting the processing of personal data, including genetic, biometric or health data. The GDPR provides for penalties for noncompliance of up to the greater of €20 million or four percent of worldwide annual revenues. The GDPR applies extraterritorially, and we may be subject to the GDPR because of our data processing activities that involve the personal data of individuals located in the EU, such as in connection with any EU clinical trials. GDPR regulations may impose additional responsibility and liability in relation to the personal data that we process and we may be required to put in place additional mechanisms to ensure compliance with the new data protection rules. Additionally, the UK has implemented legislation that substantially implements the GDPR ("UK GDPR"), with penalties for noncompliance of up to the greater of £17.5 million or four percent of worldwide revenues. Aspects of UK data protection laws and regulations remain unclear. On June 28, 2021, the European Commission announced a decision of "adequacy" concluding that the UK ensures an equivalent level of data protection to the GDPR, which provides some relief regarding the legality of continued personal data flows from the European Economic Area ("EEA") to the UK. Some uncertainty remains, however, as this adequacy determination must be renewed after four years and may be modified or revoked in the interim. We cannot fully predict how UK GDPR and data protection laws or regulations may develop in the medium-to-long term nor the effects of divergent laws and guidance regarding how data transfer to and from the UK will be regulated.

We may incur liabilities, expenses, costs, and other operational losses under the GDPR and the UK GDPR as well as privacy and data protection laws of Switzerland, the United Kingdom, and applicable EU Member States. We may find it necessary or appropriate to make additional changes to the ways we or our service providers collect, disclose, transfer, and otherwise process data within the EEA, Switzerland and the UK. This may be onerous and may interrupt or delay our development activities, and adversely affect our business, financial condition, results of operations and prospects.

Further, various states, such as California and Massachusetts, have implemented similar privacy laws and regulations that impose restrictive requirements regulating the use and disclosure of health information and other personally identifiable information. These laws and regulations are not necessarily preempted by HIPAA, particularly if a state affords greater protection to individuals than HIPAA. Where state laws are more protective, we must comply with the stricter provisions. In addition to fines and penalties imposed upon violators, some of these state laws also afford private rights of action to individuals who believe their personal information has been misused. For example, California has enacted legislation, the California Consumer Privacy Act ("CCPA"), that, among other things, requires covered companies to provide new disclosures to California consumers, and affords such consumers new abilities to opt-out of certain sales of personal information. The CCPA became effective on January 1, 2020. Some observers have noted the CCPA could be the beginning of a trend toward more stringent privacy legislation throughout the United States, as evidenced by the recent Virginia Consumer Data Protection Act, enacted March 2021, the Colorado Privacy Act, enacted June 2021, the Utah Consumer Privacy Act, enacted March 2022, and the Connecticut Act Concerning Personal Data Privacy and Online Monitoring, enacted May 2022. The CCPA, as amended and expanded by the California Privacy Rights Act ("CPRA"), requires covered companies to provide new disclosures to individuals and consumers in California, and afford such individuals and consumers new data protection rights, including the ability to opt-out of certain sales of personal information. The GDPR, UK GDPR, CCPA, CPRA and many other federal, state, and foreign 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. The U.S. federal government is also contemplating federal privacy legislation. Additionally, the interplay of federal and state laws may be subject to varying interpretations by courts and government agencies, creating complex compliance issues for us and data we receive, use and share, potentially exposing us to additional expense, adverse publicity and liability. We are working to comply with the GDPR, UK GDPR, CCPA, CPRA 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. These and future laws and regulations may increase our compliance costs and potential liability.

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

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

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

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

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

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

Our business activities may be subject to the Foreign Corrupt Practices Act of 1977, as amended (the "FCPA"), and similar anti-bribery or anti-corruption laws, regulations or rules of other countries in which we operate, including the U.K. Bribery Act. The FCPA generally prohibits offering, promising, giving, or authorizing others to give anything of value, either directly or indirectly, to a non-U.S. government official in order to influence official action, or otherwise obtain or retain business. The FCPA also requires public companies to make and keep books and records that accurately and fairly reflect the transactions of the corporation and to devise and maintain an adequate system of internal accounting controls. Our business is heavily regulated and therefore involves significant interaction with public officials, including officials of non-U.S. governments. Additionally, in many other countries, the health care providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, our dealings with these prescribers and purchasers are subject to regulation under the FCPA. Recently the Securities and Exchange Commission (the "SEC"), and Department of Justice have increased their FCPA enforcement activities with respect to biotechnology and pharmaceutical companies. There is no certainty that all of our employees, agents, contractors, or collaborators, or those of our affiliates, will comply with all applicable laws and regulations, particularly given the high level of complexity of these laws. Violations of these laws and regulations could result in fines, criminal sanctions against us, our officers, or our employees, the closing down of our facilities, requirements to obtain export licenses, cessation of business activities in sanctioned countries, implementation of compliance programs, and prohibitions on the conduct of our business. Any such violations could include prohibitions on our ability to offer our products in one or more countries and could materially damage our reputation, our brand, our international expansion efforts, our ability to attract and retain employees, and our business, prospects, operating results, and financial condition.

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

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

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes. Average review times at the FDA have fluctuated in recent years as a result. In addition, government funding of the SEC and other government agencies on which our operations may rely, including those that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable. Disruptions at the FDA and other government agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, in 2018 and 2019, the U.S. government shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical FDA, SEC and other government employees and stop critical activities. Separately, in response to the COVID-19 pandemic, since March 2020 when foreign and domestic inspections of facilities were largely placed on hold, the FDA has been working to resume routine surveillance, bioresearch monitoring and pre-approval inspections on a prioritized basis. The FDA has developed a rating system to assist in determining when and where it is safest to conduct prioritized domestic inspections. In 2020 and 2021, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. While the FDA has largely caught up with domestic preapproval inspections, it continues to work through its backlog of foreign inspections. However, if a prolonged government shutdown or other disruption occurs, including due to travel restrictions, foreign COVID-19 related policies, staffing shortages, or public health reasons, it could significantly impact the ability of the FDA or other regulatory authorities to timely review and process our regulatory submissions, or to provide feedback on our clinical development plans, which could have a material adverse effect on our business. Further, in our operations as a public company, future government shutdowns or other disruptions to normal operations could impact our ability to access the public markets and obtain the funding necessary to properly capitalize and continue our operations.

Risks Related to Our Reliance on Third Parties

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

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

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

- collaborators generally have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not properly obtain, maintain, enforce, or defend intellectual property or proprietary rights relating to our product candidates or research programs or may use our proprietary information in such a way as to expose us to potential litigation or other intellectual property related proceedings, including proceedings challenging the scope, ownership, validity and enforceability of our intellectual property;
- collaborators may own or co-own intellectual property covering our product candidates or research programs that results from our collaboration with them, and in such cases, we may not have the exclusive right to commercialize such intellectual property or such product candidates or research programs;
- we may need the cooperation of our collaborators to enforce or defend any intellectual property we contribute to or that arises out of our collaborations, which may not be provided to us;
- collaborators may control certain interactions with regulatory authorities, which may impact on our ability to obtain and maintain regulatory approval of our products candidates;
- disputes may arise between the collaborators and us that result in the delay or termination of the research, development, or commercialization of our product candidates or research programs or that result in costly litigation or arbitration that diverts management attention and resources;
- collaborators may decide to not pursue development and commercialization of any product candidates we develop or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborator's strategic focus or available funding or external factors such as an acquisition that diverts resources or creates competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials, or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates or research programs if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- collaborators may restrict us from researching, developing or commercializing certain products or technologies without their involvement;
- collaborators with marketing and distribution rights to one or more product candidates may not commit sufficient resources to the marketing and distribution of such product candidates;
- we may lose certain valuable rights under circumstances identified in our collaborations, including if we undergo a change of control;
- collaborators may grant sublicenses to our technology or product candidates or undergo a change of control and the sublicensees or new owners may decide to take the collaboration in a direction which is not in our best interest;

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

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

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

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

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

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

Our third-party service providers are not our employees, and we are therefore unable to directly monitor whether or not they devote sufficient time and resources to our clinical and nonclinical programs. These third-party service providers may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other drug development activities that could harm our competitive position. If these third parties do not successfully carry out their contractual duties, meet expected deadlines, or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for any product candidates we may develop and will not be able to, or may be delayed in our efforts to, successfully commercialize our medicines.

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

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

Although we have initiated the build-out of our Utah site to expand our clinical manufacturing capabilities for biologic therapeutics, we do not have any operational 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 some or all of our materials 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 U.S. export control regulations, 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 a need to replace current third-party manufacturers including the possibility of supply delays, 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 many components 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.

Further, we have in the past and may in the future experience delayed shipments of raw materials due to interruptions relating to the aforementioned events. We may be unable to find a sufficient alternative supply channel in a reasonable time or on commercially reasonable terms. Any performance failure on the part of our suppliers could delay the development and potential commercialization of our product candidates, including limiting supplies necessary for clinical trials and regulatory approvals, which would have a material adverse effect on our business.

Risks Related to Our Intellectual Property

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

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

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

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

The patent prosecution process is expensive, time-consuming, and complex, and we may not be able to file, prosecute, maintain, enforce, or license all necessary or desirable patent applications at a reasonable cost or in a timely manner, including delays as a result of the COVID-19 pandemic impacting our or our licensors' operations. It is also possible that we will fail to identify patentable aspects of our research and development output in time to obtain patent protection. Although we enter into nondisclosure and confidentiality agreements with parties who have access to confidential or patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, CROs, contract manufacturers, consultants, advisors, and other third parties, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. In addition, our ability to obtain and maintain valid and enforceable patents depends on whether the differences between our inventions and the prior art allow our inventions to be patentable over the prior art. Furthermore, publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we or our licensors were the first to make the inventions claimed in any of our owned or licensed patents or pending patent applications, or that we or our licensors were the first to file for patent protection of such inventions.

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

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

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

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

In addition, given the amount of time required for the development, testing, and regulatory review of new product candidates, patents protecting such product candidates might expire before or shortly after such product candidates are commercialized. As a result, our intellectual property may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

Some of our owned and in-licensed patents and patent applications are, and may in the future be, co-owned with third parties. For example, we currently, and may in the future, co-own certain patents and patent applications relating to our BBB platform technology with F-star. In addition, certain of our licensors co-own the patents and patent applications we in-license with other third parties with whom we do not have a direct relationship. Our exclusive rights to certain of these patents and patent applications are dependent, in part, on inter-institutional or other operating agreements between the joint owners of such patents and patent applications, who are not parties to our license agreements. If our licensors do not have exclusive control of the grant of licenses under any such third-party co-owners' interest in such patents or patent applications or we are otherwise unable to secure such exclusive rights, such co-owners may be able to license their rights to other third parties, including our competitors, and our competitors could market competing products and technology. In addition, we may need the cooperation of any such co-owners of our patents in order to enforce such patents against third parties, and such cooperation may not be provided to us. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations and growth prospects.

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

We are heavily reliant upon licenses to certain patent rights and proprietary technology from third parties that are important or necessary to the development of our BBB platform technology and product candidates. For example, in June 2016, we entered into a license agreement with Genentech pursuant to which we received an exclusive license to certain of Genentech's intellectual property relating to our LRRK2 program, including our BIIB122/DNL151 product candidate.

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

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

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

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

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

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

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

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

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

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

Filing, prosecuting, and defending patents on our BBB platform technology, product candidates and other technologies in all countries throughout the world would be prohibitively expensive, and the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Further, our ability to pursue patents throughout the world may be delayed or affected due to the COVID-19 global pandemic. 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. In Europe, no earlier than October 1, 2022, European applications will soon have the option, upon grant of a patent, of becoming a Unitary Patent which will be subject to the jurisdiction of the Unitary Patent Court ("UPC"). This will be a significant change in European patent practice. As the UPC is a new court system, there is no precedent for the court, increasing the uncertainty. 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.

Geopolitical actions in the United States and in foreign countries could increase the uncertainties and costs surrounding the prosecution or maintenance of our patent applications or those of any current or future licensors and the maintenance, enforcement or defense of our issued patents or those of any current or future licensors. For example, the United States and foreign government actions related to Russia's invasion of Ukraine may limit or prevent filing, prosecution, and maintenance of patent applications in Russia. Government actions may also prevent maintenance of issued patents in Russia. These actions could result in abandonment or lapse of our patents or patent applications, resulting in partial or complete loss of patent rights in Russia. If such an event were to occur, it could have a material adverse effect on our business. In addition, a decree was adopted by the Russian government in March 2022, allowing Russian companies and individuals to exploit inventions owned by patentees that have citizenship or nationality in, are registered in, or predominately have primary place of business or profit-making activities in the United States and other countries that Russia has deemed unfriendly without consent or compensation. Consequently, we may be unable to prevent third parties from practicing our inventions in Russia or from selling or importing products made using our inventions in and into Russia. Accordingly, our competitive position may be impaired, and our business, financial condition, results of operations and prospects may be adversely affected.

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.

Geopolitical actions in the United States and in foreign countries could prevent us from continuing to make these periodic payments in certain locations. For example, the United States and foreign government actions related to Russia's invasion of Ukraine may limit our ability to make or prevent us from making these payments in Russia. These actions could result in abandonment or lapse of our patents or patent applications, resulting in partial or complete loss of patent rights in Russia. If such an event were to occur, it could have a material adverse effect on our business.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Intellectual property rights do not necessarily address all potential threats.

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

- others may be able to make products that are similar to our product candidates or utilize similar technology but that are not covered by the claims of the patents that we license or may own;
- we, or our current or future licensors or collaborators, might not have been the first to make the inventions covered by the issued patent or pending patent application that we license or own now or in the future;
- we, or our current or future licensors or collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our owned or licensed intellectual property rights;
- it is possible that our current or future pending owned or licensed patent applications will not lead to issued patents;
- issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors or other third parties;

- our competitors or other third parties might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents of others may harm our business; and
- we may choose not to file a patent in order to maintain certain trade secrets or know-how, and a third party may subsequently file a patent covering such intellectual property.

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

Risks Related to Our Operations

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

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

We primarily 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. In response to increased competition in the labor market and rising inflation, we may need to adjust employee cash compensation, which would affect our operating costs and margins, or employee equity compensation, which would affect our outstanding share count and cause dilution to our existing stockholders.

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

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

As of September 30, 2022, we had approximately 413 employees, all of whom were full-time. As our development plans and strategies develop, we must add a significant number of additional managerial, operational, financial, and other personnel. Future growth will impose significant added responsibilities on members of management, including:

- identifying, recruiting, integrating, retaining, and motivating additional employees;

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

Our future financial performance and our ability to continue to develop and, if approved, commercialize our product candidates will depend, in part, on our ability to effectively manage any future growth. Our management may also have to divert a disproportionate amount of its attention away from day-to-day activities in order to manage these growth activities.

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. In August 2020, we entered into the Provisional Biogen Collaboration Agreement, and in connection therewith we sold 13,310,243 shares of our common stock to Biogen in September 2020 for an aggregate purchase price of \$465.0 million. 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 or incidents that could compromise the confidentiality, integrity, and availability of such systems and data, expose us to liability, and affect our reputation.

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

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

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

Our operations, and those of our third-party research institution collaborators, CROs, CDMOs, suppliers, and other contractors and consultants, could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, health epidemics such as COVID-19, 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.

The majority 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, rising interest rates or political instability in certain non-U.S. economies and markets;
- differing and changing regulatory requirements in non-U.S. countries;
- challenges enforcing our contractual and intellectual property rights, especially in those foreign countries that do not respect and protect intellectual property rights to the same extent as the United States;
- difficulties in compliance with non-U.S. laws and regulations;
- changes in non-U.S. regulations and customs, tariffs and trade barriers;
- changes in non-U.S. currency exchange rates and currency controls;
- changes in a specific country's or region's political or economic environment;
- trade protection measures, import or export licensing requirements or other restrictive actions by U.S. or non-U.S. governments;
- negative consequences from changes in tax laws;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- difficulties associated with staffing and managing international operations, including differing labor relations;
- potential liability under the FCPA, UK Bribery Act or comparable foreign laws;
- business interruptions resulting from geopolitical actions, including war, such as Russia's invasion of Ukraine, and terrorism, natural disasters including earthquakes, typhoons, floods and fires, or health epidemics such as COVID-19; and
- cyberattacks, which are growing in frequency, sophistication and intensity, and are becoming increasingly difficult to detect.

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

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

As of December 31, 2021, we had federal net operating loss carryforwards of approximately \$232.3 million, federal research and development tax credit carryforwards of approximately \$31.7 million, and orphan tax credit carryforwards of approximately \$9.3 million, some of which will begin to expire in 2035. Under Sections 382 and 383 of the United States Internal Revenue Code of 1986, as amended, (the "Code"), if a corporation undergoes an "ownership change" (generally defined as a greater than 50-percentage-point cumulative change (by value) in the equity ownership of certain stockholders over a rolling three-year period), the corporation's ability to use its pre-change net operating loss carryforwards and other pre-change tax attributes to offset its post-change taxable income or taxes may be limited. We may have experienced ownership changes in the past, and we may also experience ownership changes in the future as a result of subsequent shifts in our stock ownership (including in connection with this offering), some of which are outside our control. As a result, our ability to use our pre-change net operating loss carryforwards and other pre-change tax attributes to offset post-change taxable income or taxes may be subject to limitation.

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

The rules dealing with U.S. federal, state and local income taxation are constantly under review by persons involved in the legislative process and by the IRS and the U.S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect our stockholders or us. In recent years, many such changes have been made, and changes are likely to continue to occur in the future. For example, in August 2022, the United States enacted the Inflation Reduction Act, which implemented a 15% minimum tax on book income for certain companies and introduced a 1% excise tax on stock buybacks. In addition, the current tax administration has proposed changes to the orphan drug tax credit. We cannot predict whether, when, in what form, or with what effective dates, tax laws, regulations and rulings may be enacted, promulgated or decided, which could result in an increase in our, or our stockholders', tax liability or require changes in the manner in which we operate in order to minimize increases in our tax liability.

Risks Related to Ownership of Our Common Stock

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

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

- the success of existing or new competitive products or technologies;
- the timing and results of clinical trials for our current product candidates and any future product candidates that we may develop;
- commencement or termination of collaborations for our product development and research programs;
- failure to achieve development, regulatory or commercialization milestones under our collaborations;
- failure or discontinuation of any of our product development and research programs;
- failure to develop our BBB platform technology;

- results of preclinical studies, clinical trials, or regulatory approvals of product candidates of our competitors, or announcements about new research programs or product candidates of our competitors;
- regulatory or legal developments in the United States and other countries;
- developments or disputes concerning patent applications, issued patents, or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to any of our research programs, clinical development programs, or product candidates that we may develop;
- the results of our efforts to develop additional product candidates or products;
- actual or anticipated changes in estimates as to financial results, development timelines, or recommendations by securities analysts;
- announcement or expectation of additional financing efforts;
- sales of our common stock by us, our insiders, or other stockholders;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in estimates or recommendations by securities analysts, if any, that cover our stock;
- changes in the structure of healthcare payment systems;
- adoption of new accounting standards or changes in accounting standards;
- ineffectiveness of our internal controls;
- significant lawsuits, including patent or stockholder litigation;
- market conditions in the pharmaceutical and biotechnology sectors; and
- general economic, industry, and market conditions, including those caused by the ongoing COVID-19 pandemic.

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 or if we fail to meet the expectations of analysts, the price of our stock could decline. If one or more of these analysts cease to cover our stock, we could lose visibility in the market for our stock, which in turn could cause our stock price or trading volume to decline.

Sales of substantial amounts of our common stock in the public markets, or the perception that such sales might occur, could cause the market price of our common stock to decline significantly, even if our business is doing well.

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

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

Certain holders of shares of our common stock have rights, subject to conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. In addition, Biogen is entitled to certain registration rights with respect to the 13,310,243 shares of common stock purchased, if such shares cannot be resold without restriction pursuant to Rule 144 promulgated under the Securities Act. Registration of these shares under the Securities Act would result in the shares becoming freely tradeable in the public market, subject to the restrictions of Rule 144 in the case of our affiliates. Any sales of securities by these stockholders or the perception that sales will be made in the public market, could have a material adverse effect on the market price for our common stock.

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

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

We may seek additional capital through a combination of public and private equity offerings, debt financings, strategic partnerships and alliances and licensing arrangements. For example, in August 2020, we entered into the Provisional Biogen Collaboration Agreement, and in connection therewith issued and sold 13,310,243 shares of our common stock to Biogen in September 2020 for an aggregate purchase price of \$465.0 million. We, and indirectly, our stockholders, will bear the cost of issuing and servicing all such securities.

In January 2020, we sold 9.0 million shares of common stock in an underwritten follow-on offering pursuant to a shelf registration statement filed in March 2019. We filed a second shelf registration statement on February 28, 2022 and simultaneously entered into an equity distribution agreement with Goldman Sachs & Co. LLC, SVB Securities LLC, and Cantor Fitzgerald & Co., as sales agents, to establish an at-the-market facility pursuant to which we may offer and sell from time to time up to \$400.0 million shares of our common stock. Further, the shelf registration allows us to sell, from time to time, an unspecified number of additional shares of common stock; shares of preferred stock; debt securities; warrants to purchase shares of common stock, preferred stock, or other securities; purchase contracts; and units representing two or more of the foregoing securities.

Our decision to issue debt or equity securities in any future offering will depend on market conditions and other factors beyond our control, and therefore 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. In addition, any sales of our common stock or other securities under our shelf registration statement, including pursuant to at-the-market offerings, could put downward pressure on our stock price. Additionally, 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.

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

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

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

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

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

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

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

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

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

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

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

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

- establish that our board of directors is divided into three classes, Class I, Class II and Class III, with each class serving staggered three-year terms;
- provide that vacancies on our board of directors may be filled only by a majority of directors then in office, even though less than a quorum;
- provide that our directors may only be removed for cause;
- eliminate cumulative voting in the election of directors;
- authorize our board of directors to issue shares of preferred stock and determine the price and other terms of those shares, including preferences and voting rights, without stockholder approval;
- provide our board of directors with the exclusive right to elect a director to fill a vacancy or newly created directorship;
- permit stockholders to only take actions at a duly called annual or special meeting and not by written consent;
- prohibit stockholders from calling a special meeting of stockholders;

- require that stockholders give advance notice to nominate directors or submit proposals for consideration at stockholder meetings;
- authorize our board of directors, by a majority vote, to amend the bylaws; and
- require the affirmative vote of at least 66 2/3% or more of the outstanding shares of common stock to amend many of the provisions described above.

In addition, Section 203 of the General Corporation Law of the State of Delaware, (the "DGCL"), prohibits a publicly-held Delaware corporation from engaging in a business combination with an interested stockholder, generally a person which together with its affiliates owns, or within the last three years has owned, 15.0% of our voting stock, for a period of three years after the date of the transaction in which the person became an interested stockholder, unless the business combination is approved in a prescribed manner.

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

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

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

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

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

These exclusive-forum provisions may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers, or other employees, which may discourage lawsuits against us and our directors, officers, and other employees. If a court were to find either exclusive-forum provision in our amended and restated certificate of incorporation to be inapplicable or unenforceable in an action or we do not enforce such provision, we may incur additional costs associated with resolving the dispute in other jurisdictions, which could seriously harm our business.

Risks Related to this Offering

We will have broad discretion in how we use the net proceeds of this offering. We may not use these proceeds effectively, which could affect our results of operations and cause our stock price to decline.

Although we currently intend to use the net proceeds from this offering in the manner described in the section entitled "Use of Proceeds" in this prospectus supplement, we will have considerable discretion in the application of the net proceeds of this offering. We may use the net proceeds for purposes that do not yield a significant return or any return at all for our stockholders. In addition, pending their use, we may invest the net proceeds from this offering in a manner that does not produce income or that loses value. If we do not invest or apply the net proceeds from this offering in ways that enhance stockholder value, we may fail to achieve expected financial results, which could cause our stock price to decline.

You may experience immediate and substantial dilution in the book value per share of the common stock you purchase.

Because the price per share at which shares of our common stock are sold in this offering may be substantially higher than the net tangible book value per share of our common stock, you may suffer immediate and substantial dilution in the net tangible book value of the common stock you purchase in this offering. For a further description of the dilution that you will experience immediately after this offering, see the section in this prospectus supplement entitled "Dilution."

Resales of our common stock in the public market by our stockholders as a result of this offering may cause the market price of our common stock to fall.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. The issuance of these new shares of our common stock in this offering could result in resales of our common stock by our current stockholders concerned about the potential ownership dilution of their holdings. In turn, these resales could have the effect of depressing the market price for our common stock.

USE OF PROCEEDS

We estimate that the net proceeds from this offering will be approximately \$ _____ based on the sale by us of _____ shares of our common stock offered hereby, or approximately \$ _____ if the underwriters exercise in full their option to purchase an additional _____ shares of common stock, at the public offering price of \$ _____ per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

We intend to use the net proceeds of this offering to fund the following:

- The progression of multiple clinical programs into late-stage trials, including DNL310 (ETV:IDS), DNL343 (eIF2B activator), BIIB122/DNL151 (LRRK2 inhibitor) and SAR443820/DNL788 (RIPK1 inhibitor);
- Potential acceleration of commercial launch readiness in the U.S. and other key global markets;
- Expansion of the TV platform, including development of the OTV platform that will enable broad distribution of ASOs throughout the brain;
- Continued development and expansion of the early-stage portfolio, including advancing three additional NMEs into the clinic; and
- Build-out and expansion of in-house clinical manufacturing capabilities for biologic therapeutics, including the manufacture of materials for toxicology studies and drug substance for early human clinical studies.

We expect to use any remaining net proceeds from this offering for general and administrative expenses, potential future development programs, early-stage research and development, capital expenditures and working capital and other general corporate purposes.

Our expected use of net proceeds from this offering represents our current intentions based upon our present plans and business condition. As of the date of this prospectus supplement, we cannot predict with certainty all of the particular uses for the net proceeds to be received upon the completion of this offering or the amounts that we will actually spend on the uses set forth above. We may also use a portion of the net proceeds to in-license, acquire or invest in complementary businesses, technologies, products or assets. Due to the many variables inherent to drug development at this time, such as the timing of patient enrollment and evolving regulatory requirements, we cannot currently predict the stage of development we expect the net proceeds of this offering to achieve for our clinical studies and product candidates.

The amount and timing of our actual expenditures will depend upon numerous factors, including the results of our research and development efforts, the timing and success of preclinical studies, our ongoing clinical studies or clinical studies we may commence in the future and the timing of regulatory submissions. As a result, our management will have broad discretion over the use of the net proceeds from this offering.

Pending the use of the net proceeds from this offering, we intend to invest the net proceeds in short to intermediate-term fixed income securities.

DILUTION

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

Our historical net tangible book value as of June 30, 2022 was \$884.4 million, or \$7.18 per share of our common stock. Our historical net tangible book value is the amount of our total tangible assets less our total liabilities. Historical net tangible book value per share represents historical net tangible book value divided by the number of shares of our common stock outstanding as of June 30, 2022.

After giving further effect to the sale of _____ shares of common stock in this offering at the public offering price of _____ per share, and after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of June 30, 2022 would have been approximately _____, or approximately _____ per share. This represents an immediate increase in as adjusted net tangible book value per share of _____ to our existing stockholders and an immediate dilution in as adjusted net tangible book value per share of approximately _____ to new investors purchasing common stock in this offering. Dilution per share to new investors purchasing common stock in this offering is determined by subtracting as adjusted net tangible book value per share after this offering from the public offering price per share paid by new investors.

The following table illustrates this per share dilution:

Public offering price per share	
Historical net tangible book value per share as of June 30, 2022	\$ 7.18
Increase in net tangible book value per share attributable to new investors	_____
As adjusted net tangible book value per share after this offering	_____
Dilution per share to new investors	_____

The foregoing table and discussion is based on 123,157,278 shares of common stock outstanding as of June 30, 2022, and excludes:

- 15,158,522 shares of common stock issuable upon the exercise of stock options outstanding as of June 30, 2022, at a weighted average exercise price of \$26.96 per share;
- 2,898,742 shares of common stock issuable upon the vesting of restricted stock units outstanding as of June 30, 2022;
- up to an aggregate of \$400.0 million of shares of common stock that may be sold under our “at-the-market” program with Goldman Sachs & Co. LLC, SVB Securities LLC, and Cantor Fitzgerald & Co.;
- 10,636,762 shares of common stock reserved for future issuance under the 2017 Plan as of June 30, 2022; and
- 4,568,809 shares of common stock reserved for future issuance under our 2017 ESPP as of June 30, 2022

If the underwriters exercise in full their option to purchase up to _____ additional shares of common stock at the public offering price of \$ _____ per share, the as adjusted net tangible book value after this offering would be \$ _____ per share, representing an increase in net tangible book value of \$ _____ per share to existing stockholders and immediate dilution in net tangible book value of _____ per share to investors purchasing our common stock in this offering at the public offering price.

To the extent that any options are exercised, any restricted stock units are settled, any new awards are issued under our equity incentive plans, or we otherwise issue additional shares of common stock in the future (including shares issued in connection with acquisitions), there will be further dilution to new investors.

In addition, we may choose to raise additional capital due to market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans. To the extent that additional capital is raised through the sale of equity or convertible debt securities, the issuance of these securities could result in further dilution to our stockholders.

DIVIDEND POLICY

We have never declared or paid cash dividends on our common stock. We currently intend to retain all available funds and any future earnings, if any, to fund the development and expansion of our business and we do not anticipate paying any cash dividends in the foreseeable future. Any future determination to pay dividends will be made at the discretion of our board of directors.

DESCRIPTION OF CAPITAL STOCK

The following is a summary of our capital stock and provisions of our amended and restated certificate of incorporation, amended and restated bylaws and investors' rights agreement, as each is in effect as of the date of this prospectus supplement. This summary does not purport to be complete and is qualified in its entirety by the provisions of our amended and restated certificate of incorporation, amended and restated bylaws and investors' rights agreement, copies of which are incorporated by reference as exhibits to the accompanying registration statement. References in this section to "the company," "we," "us" and "our" refer to Denali Therapeutics Inc. and not to any of its subsidiaries.

Our authorized capital stock consists of 440,000,000 shares, with a par value of \$0.01 per share, of which:

- 400,000,000 shares are designated as common stock; and
- 40,000,000 shares are designated as preferred stock.

Common Stock

Outstanding Shares

As of October 3, 2022, we had 123,796,438 shares of common stock outstanding and approximately 147 record holders of our common stock.

Voting Rights

Each holder of common stock is entitled to one vote for each share on all matters submitted to a vote of the stockholders, including the election of directors. Our amended and restated certificate of incorporation and amended and restated bylaws do not provide for cumulative voting rights. Because of this, the holders of a plurality of the shares of common stock entitled to vote in any election of directors can elect all of the directors standing for election, if they should so choose. With respect to matters other than the election of directors, at any meeting of the stockholders at which a quorum is present or represented, the affirmative vote of a majority of the voting power of the shares present in person or represented by proxy at such meeting and entitled to vote on the subject matter shall be the act of the stockholders, except as otherwise required by law. The holders of a majority of the stock issued and outstanding and entitled to vote, present in person or represented by proxy, shall constitute a quorum for the transaction of business at all meetings of the stockholders.

Dividends

Subject to preferences that may be applicable to any then-outstanding preferred stock, holders of our common stock are entitled to receive dividends, if any, as may be declared from time to time by our board of directors out of legally available funds.

Liquidation

In the event of our liquidation, dissolution or winding up, holders of our common stock will be entitled to share ratably in the net assets legally available for distribution to stockholders after the payment of all of our debts and other liabilities and the satisfaction of any liquidation preference granted to the holders of any then-outstanding shares of preferred stock.

Rights and Preferences

Holders of our common stock have no preemptive, conversion, subscription or other rights, and there are no redemption or sinking fund provisions applicable to our common stock. The rights, preferences and privileges of the holders of our common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of our preferred stock that we may designate in the future.

Fully Paid and Nonassessable

All of our outstanding shares of common stock are, and the shares of common stock to be issued in this offering, upon payment and delivery in accordance with the underwriting agreement, will be fully paid and nonassessable.

Preferred Stock

Our amended and restated certificate of incorporation contains provisions that permit our board of directors to issue, without any further vote or action by the stockholders, shares of preferred stock in one or more series and, with respect to each such series, to fix the number of shares constituting the series and the designation of the series, the voting rights (if any) of the shares of the series, and the powers, preferences or relative, participation, optional and other special rights, if any, and any qualifications, limitations or restrictions, of the shares of such series.

Anti-Takeover Effects of Certain Provisions of Delaware Law, Our Amended and Restated Certificate of Incorporation and Our Amended and Restated Bylaws

Certain provisions of Delaware law and certain provisions included in our amended and restated certificate of incorporation and amended and restated bylaws summarized below may be deemed to have an anti-takeover effect and may delay, deter, or prevent a tender offer or takeover attempt that a stockholder might consider to be in its best interests, including attempts that might result in a premium being paid over the market price for the shares held by stockholders.

Classified Board of Directors

Our amended and restated certificate of incorporation provides that our board of directors is divided into three classes, designated Class I, Class II, and Class III. The directors in each class serve for a three-year term, one class being elected each year by our stockholders, with staggered three-year terms. Only one class of directors is elected at each annual meeting of our stockholders, with the other classes continuing for the remainder of their respective three-year terms. Because our stockholders do not have cumulative voting rights, our stockholders holding a majority of the shares of common stock outstanding are able to elect all of our directors.

Removal of Directors

Our amended and restated certificate of incorporation provides that stockholders may only remove a director for cause by a vote of no less than a majority of the shares present in person or by proxy at the meeting and entitled to vote.

Director Vacancies

Our amended and restated certificate of incorporation authorizes only our board of directors to fill vacant directorships.

No Cumulative Voting

Our amended and restated certificate of incorporation provides that stockholders do not have the right to cumulate votes in the election of directors.

Special Meetings of Stockholders

Our amended and restated certificate of incorporation and amended and restated bylaws provide that, except as otherwise required by law, special meetings of the stockholders may be called only by an officer at the request of a majority of our board of directors, by the chairperson of our board of directors, or by our Chief Executive Officer.

Advance Notice Procedures for Director Nominations

Our amended and restated bylaws provide that stockholders seeking to nominate candidates for election as directors at an annual or special meeting of stockholders must provide timely notice thereof in writing. To be timely, a stockholder's notice generally must be delivered to and received at our principal executive offices before notice of the meeting is issued by the secretary of the company, with such notice being served not less than 90 nor more than 120 days before the meeting. Although our amended and restated bylaws do not give our board of directors the power to approve or disapprove stockholder nominations of candidates to be elected at an annual meeting, our amended and restated bylaws may have the effect of precluding the conduct of certain business at a meeting if the proper procedures are not followed or may discourage or deter a potential acquirer from conducting a solicitation of proxies to elect its own slate of directors or otherwise attempting to obtain control of the company.

Action by Written Consent

Our amended and restated certificate of incorporation and amended and restated bylaws provide that any action to be taken by the stockholders must be effected at a duly called annual or special meeting of stockholders and may not be effected by written consent.

Amending our Certificate of Incorporation and Bylaws

Our amended and restated certificate of incorporation may be amended or altered in any manner provided by the DGCL. Our amended and restated bylaws may be adopted, amended, altered, or repealed by stockholders only upon approval of at least majority of the voting power of all the then outstanding shares of the common stock, except for any amendment of the above provisions, which would require the approval of a two-thirds majority of our then outstanding common stock. Additionally, our amended and restated certificate of incorporation provides that our bylaws may be amended, altered, or repealed by our board of directors.

Authorized but Unissued Shares

Our authorized but unissued shares of common stock and preferred stock are available for future issuances without stockholder approval, except as required by the listing standards of Nasdaq, and could be utilized for a variety of corporate purposes, including future offerings to raise additional capital, acquisitions and employee benefit plans. The existence of authorized but unissued and unreserved common stock and preferred stock could render more difficult or discourage an attempt to obtain control of the company by means of a proxy contest, tender offer, merger or otherwise.

Exclusive Jurisdiction

Our amended and restated certificate of incorporation provide that, unless we consent to the selection of an alternative forum, the Court of Chancery of the State of Delaware shall be the sole and exclusive forum for any derivative action or proceeding brought on our behalf, any action asserting a claim of breach of fiduciary duty, any action asserting a claim arising pursuant to the DGCL, any action regarding our amended and restated certificate of incorporation or our amended and restated bylaws or any action asserting a claim against us that is governed by the internal affairs doctrine.

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

Business Combinations with Interested Stockholders

We are governed by Section 203 of the DGCL. Subject to certain exceptions, Section 203 of the DGCL prohibits a public Delaware corporation from engaging in a business combination (as defined in such section) with an “interested stockholder” (defined generally as any person who beneficially owns 15% or more of the outstanding voting stock of such corporation or any person affiliated with such person) for a period of three years following the time that such stockholder became an interested stockholder, unless (i) prior to such time the board of directors of such corporation approved either the business combination or the transaction that resulted in the stockholder becoming an interested stockholder; (ii) upon consummation of the transaction that resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of such corporation at the time the transaction commenced (excluding for purposes of determining the voting stock of such corporation outstanding (but not the outstanding voting stock owned by the interested stockholder) those shares owned (A) by persons who are directors and also officers of such corporation and (B) by employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer); or (iii) at or subsequent to such time the business combination is approved by the board of directors of such corporation and authorized at a meeting of stockholders (and not by written consent) by the affirmative vote of at least 66 2/3% of the outstanding voting stock of such corporation not owned by the interested stockholder.

Limitation on Liability and Indemnification

Our amended and restated certificate of incorporation and our amended and restated bylaws provide that we must indemnify our directors and officers to the fullest extent authorized by the DGCL. We are expressly authorized to carry, and we do carry, directors’ and officers’ insurance providing coverage for our directors, officers and certain employees for some liabilities. We believe that these indemnification provisions and insurance are useful to attract and retain qualified directors and executive officers.

The limitation on liability and indemnification provisions in our amended and restated certificate of incorporation and amended and restated bylaws may discourage stockholders from bringing a lawsuit against directors for breach of their fiduciary duty. These provisions may also have the effect of reducing the likelihood of derivative litigation against directors and officers, even though such an action, if successful, might otherwise benefit us and our stockholders. In addition, your investment may be adversely affected to the extent we pay the costs of settlement and damage awards against directors and officers pursuant to these indemnification provisions.

Registration Rights

Under our investors’ rights agreement, as amended, certain holders of our common stock, or their transferees, have the right to require us to register the offer and sale of their shares or to include their shares in any registration statement we file, in each case as described below.

Demand Registration Rights

Certain holders of shares of our common stock are entitled to certain demand registration rights. At any time beginning 180 days after the date of effectiveness of our initial public offering, holders of at least a majority of the shares having registration rights then outstanding can request that we file a registration statement to register the offer and sale of their shares. We are obligated to effect only two such registrations. Each such request for registration must cover securities the anticipated aggregate public offering price of which, before payment of underwriting discounts and commissions, is at least \$10 million. These demand registration rights are subject to specified conditions and limitations, including the right of the underwriters to limit the number of shares included in any such registration under certain circumstances. If we determine that it would be seriously detrimental to us and our stockholders to effect such a demand registration, we have the right to defer such registration, not more than twice in any 12-month period, for a period of up to 60 days.

Form S-3 Registration Rights

Certain holders of shares of our common stock are entitled to certain Form S-3 registration rights. When we are eligible to file a registration statement on Form S-3, the holders of at least twenty percent of the shares having these rights then outstanding can request that we register the offer and sale of their shares of our common stock on a registration statement on Form S-3 so long as the request covers securities the anticipated aggregate public offering price of which, before payment of underwriting discounts and commissions, is at least \$5 million. These stockholders may make an unlimited number of requests for registration on a registration statement on Form S-3. However, we will not be required to effect a registration on Form S-3 if we have effected two such registrations within the 12-month period preceding the date of the request. Additionally, if we determine that it would be seriously detrimental to us and our stockholders to effect such a demand registration, we have the right to defer such registration, not more than twice in any 12-month period, for a period of up to 60 days.

Piggyback Registration Rights

Certain holders of shares of our common stock are entitled to certain “piggyback” registration rights. If we propose to register the offer and sale of shares of our common stock under the Securities Act, all holders of these shares then outstanding can request that we include their shares in such registration, subject to certain marketing and other limitations, including the right of the underwriters to limit the number of shares included in any such registration statement under certain circumstances. As a result, whenever we propose to file a registration statement under the Securities Act, other than with respect to (1) a registration related to any employee benefit plan or a corporate reorganization or other transaction covered by Rule 145 promulgated under the Securities Act, (2) a registration in which the only stock being registered is common stock issuable upon conversion of debt securities also being registered or (3) a registration on any form that does not include substantially the same information as would be required to be included in a registration statement covering the sale of our common stock, the holders of these shares are entitled to notice of the registration and have the right, subject to certain limitations, to include their shares in the registration.

Expenses of Registration

We will pay all expenses relating to any demand registrations, Form S-3 registrations and piggyback registrations, subject to specified exceptions.

Termination

The registration rights terminate upon the earliest of (1) the date that is five years after the closing of our initial public offering, (2) as to a given holder of registration rights, when such holder of registration rights can sell all of such holder’s registrable securities in a three-month period pursuant to Rule 144 promulgated under the Securities Act and (3) the closing of a deemed liquidation event.

Registration Rights of Certain Other Stockholders

One of our other stockholders, Biogen MA, Inc. (“BIMA”), and Biogen International GmbH, (“BIG”, together with BIMA, collectively, “Biogen”), also has registration rights under the standstill and stock restriction agreement between us and Biogen (the “Biogen Standstill Agreement”). Biogen (and certain of its permitted transferees) may request that we file registration statements under the Securities Act of 1933 and, upon such request and subject to certain conditions, the Company will be required to use its commercially reasonable efforts to effect any such registration. The Company is generally obligated to bear the expenses, other than underwriting discounts and sales commissions, of all of these registrations. This summary does not purport to be complete and is qualified in its entirety by the provisions of the Biogen Standstill Agreement, a copy of which has been filed as an exhibit to our Annual Report on Form 10-K for the year ended December 31, 2021.

Listing

Our common stock is listed on the Nasdaq Global Select Market under the symbol “DNL”.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Broadridge Financial Solutions, Inc. The transfer agent and registrar’s address is 51 Mercedes Way, Edgewood, NY 11717.

MATERIAL U.S. FEDERAL INCOME TAX CONSIDERATIONS FOR NON-U.S. HOLDERS OF OUR COMMON STOCK

The following is a summary of the material U.S. federal income tax consequences of the ownership and disposition of our common stock acquired in this offering by a “non-U.S. holder” (as defined below), but does not purport to be a complete analysis of all the potential tax considerations relating thereto. This summary is based upon the provisions of the United States Internal Revenue Code of 1986, as amended, or the Code, Treasury Regulations promulgated thereunder, administrative rulings and judicial decisions, all as of the date hereof. These authorities may be changed, possibly retroactively, so as to result in U.S. federal income tax consequences different from those set forth below. We have not sought, and do not intend to seek, any ruling from the Internal Revenue Service, or IRS, with respect to the statements made and the conclusions reached in the following summary, and there can be no assurance that the IRS or a court will agree with such statements and conclusions.

This summary also does not address the tax considerations arising under the laws of any non-U.S., state or local jurisdiction or under U.S. federal gift and estate tax rules, except to the limited extent set forth below. In addition, this discussion does not address tax considerations applicable to an investor’s particular circumstances or to investors that may be subject to special tax rules, including, without limitation:

- banks, insurance companies, regulated investment companies, real estate investment trusts or other financial institutions;
- persons subject to the alternative minimum tax or the tax on net investment income;
- tax-exempt organizations;
- pension plans and tax-qualified retirement plans;
- controlled foreign corporations, passive foreign investment companies and corporations that accumulate earnings to avoid U.S. federal income tax;
- brokers or dealers in securities or currencies;
- traders in securities that elect to use a mark-to-market method of tax accounting for their securities holdings;
- persons that own, or are deemed to own, more than five percent of our capital stock (except to the extent specifically set forth below);
- certain former citizens or long-term residents of the United States;
- persons who hold our common stock as a position in a hedging transaction, “straddle,” “conversion transaction” or other risk reduction transaction;
- persons who hold or receive our common stock pursuant to the exercise of any option or otherwise as compensation;
- persons subject to special tax accounting rules under Section 451 of the Code;
- persons who do not hold our common stock as a capital asset within the meaning of Section 1221 of the Code (generally, property held for investment); or
- persons deemed to sell our common stock under the constructive sale provisions of the Code.

In addition, if a partnership, entity or arrangement classified as a partnership or flow-through entity for U.S. federal income tax purposes holds our common stock, the tax treatment of a partner generally will depend on the status of the partner and upon the activities of the partnership or other entity. A partner in a partnership or other such entity that will hold our common stock should consult his, her or its own tax advisor regarding the tax consequences of the ownership and disposition of our common stock through a partnership or other such entity, as applicable.

You are urged to consult your tax advisor with respect to the application of the U.S. federal income tax laws to your particular situation, as well as any tax consequences of the purchase, ownership and disposition of our common stock arising under the U.S. federal gift or estate tax rules or under the laws of any state, local, non-U.S. or other taxing jurisdiction or under any applicable tax treaty.

Non-U.S. Holder Defined

For purposes of this discussion, you are a “non-U.S. holder” if you are a beneficial owner of our common stock that, for U.S. federal income tax purposes, is not a partnership or:

- an individual who is a citizen or resident of the United States;
- a corporation or other entity taxable as a corporation created or organized in the United States or under the laws of the United States or any political subdivision thereof, or otherwise treated as such for U.S. federal income tax purposes;
- an estate whose income is subject to U.S. federal income tax regardless of its source; or
- a trust (x) whose administration is subject to the primary supervision of a U.S. court and that has one or more U.S. persons who have the authority to control all substantial decisions of the trust or (y) that has made a valid election under applicable Treasury Regulations to be treated as a U.S. person.

Distributions

As described in the section titled “Dividend Policy,” we have never declared or paid cash dividends on our common stock, and we do not anticipate paying any dividends on our common stock following the completion of this offering. However, if we do make distributions on our common stock, those payments will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. To the extent those distributions exceed both our current and our accumulated earnings and profits, the excess will constitute a return of capital and will first reduce your basis in our common stock, but not below zero, and then will be treated as gain from the sale of stock.

Subject to the discussions below on effectively connected income and Foreign Account Tax Compliance Act, or FATCA, withholding, any dividend paid to you generally will be subject to U.S. federal withholding tax either at a rate of 30% of the gross amount of the dividend or such lower rate as may be specified by an applicable income tax treaty between the United States and your country of residence. In order to receive a reduced treaty rate, you must provide the applicable withholding agent with an IRS Form W-8BEN or W-8BEN-E or other appropriate version of IRS Form W-8 certifying qualification for the reduced rate. A non-U.S. holder of shares of our common stock eligible for a reduced rate of U.S. federal withholding tax pursuant to an income tax treaty may obtain a refund of any excess amounts withheld by filing an appropriate claim for refund with the IRS. If the non-U.S. holder holds our common stock through a financial institution or other agent acting on the non-U.S. holder’s behalf, the non-U.S. holder will be required to provide appropriate documentation to the agent, which then will be required to provide certification to the applicable withholding agent, either directly or through other intermediaries.

Dividends received by you that are treated as effectively connected with your conduct of a U.S. trade or business (and, if required by an applicable income tax treaty, such dividends are attributable to a permanent establishment or fixed base maintained by you in the United States) are generally exempt from the 30% U.S. federal withholding tax, subject to the discussion below on backup withholding and FATCA withholding. In order to obtain this exemption, you must provide the applicable withholding agent with a properly executed IRS Form W-8ECI or other applicable IRS Form W-8 properly certifying such exemption. Such effectively connected dividends, although not subject to U.S. federal withholding tax, are taxed at the same rates applicable to U.S. persons, net of certain deductions and credits. In addition, if you are a corporate non-U.S. holder, dividends you receive that are effectively connected with your conduct of a U.S. trade or business may also be subject to a branch profits tax at a rate of 30% or such lower rate as may be specified by an applicable income tax treaty between the United States and your country of residence. You should consult your tax advisor regarding the tax consequences of the ownership and disposition of our common stock, including any applicable tax treaties that may provide for different rules.

Gain on Disposition of Common Stock

Subject to the discussion below regarding backup withholding, you generally will not be required to pay U.S. federal income tax on any gain realized upon the sale or other disposition of our common stock unless:

- the gain is effectively connected with your conduct of a U.S. trade or business (and, if an applicable income tax treaty so provides, the gain is attributable to a permanent establishment or fixed base maintained by you in the United States);
- you are an individual who is present in the United States for a period or periods aggregating 183 days or more during the calendar year in which the sale or disposition occurs and certain other conditions are met; or
- our common stock constitutes a United States real property interest by reason of our status as a “United States real property holding corporation,” or USRPHC, for U.S. federal income tax purposes at any time within the shorter of the five-year period preceding your disposition of, or your holding period for, our common stock.

We believe that we are not currently and will not become a USRPHC for U.S. federal income tax purposes, and the remainder of this discussion so assumes. However, because the determination of whether we are a USRPHC depends on the fair market value of our U.S. real property interests relative to the fair market value of our U.S. and worldwide real property interests plus our other business assets, there can be no assurance that we will not become a USRPHC in the future. Even if we become a USRPHC, however, as long as our common stock is regularly traded on an established securities market, your common stock will be treated as U.S. real property interests only if you actually (directly or indirectly) or constructively hold more than five percent of such regularly traded common stock at any time during the shorter of the five-year period preceding your disposition of, or your holding period for, our common stock. We expect our stock to continue to be regularly traded on an established securities market; however, we cannot provide any assurance that our stock will be regularly traded on an established securities market in the future.

If you are a non-U.S. holder described in the first bullet above, you will be required to pay tax on the gain derived from the sale (net of certain deductions and credits) under regular U.S. federal income tax rates, and a corporate non-U.S. holder described in the first bullet above also may be subject to the branch profits tax at a 30% rate, or such lower rate as may be specified by an applicable income tax treaty. If you are an individual non-U.S. holder described in the second bullet above, you will be subject to tax at 30% (or such lower rate specified by an applicable income tax treaty) on the gain derived from the sale, which gain may be offset by U.S. source capital losses for the year, provided you have timely filed U.S. federal income tax returns with respect to such losses. You should consult your tax advisor regarding any applicable income tax or other treaties that may provide for different rules.

Our common stock beneficially owned by an individual who is not a citizen or resident of the United States (as defined for U.S. federal estate tax purposes) at the time of his or her death will generally be includable in the decedent's gross estate for U.S. federal estate tax purposes. Such stock, therefore, may be subject to U.S. federal estate tax, unless an applicable estate tax treaty provides otherwise.

Backup Withholding and Information Reporting

Generally, we must report annually to the IRS the amount of dividends paid to you, your name and address, and the amount of tax withheld, if any. A similar report will be sent to you. Pursuant to applicable income tax treaties or other agreements, the IRS may make these reports available to tax authorities in your country of residence.

Payments of dividends on or of proceeds from the disposition of our common stock made to you may be subject to information reporting and backup withholding at a current rate of 24% unless you establish an exemption, for example, by properly certifying your non-U.S. status on a properly completed IRS Form W-8BEN or W-8BEN-E or another appropriate version of IRS Form W-8. Notwithstanding the foregoing, backup withholding and information reporting may apply if the applicable withholding agent has actual knowledge, or reason to know, that you are a U.S. person.

Backup withholding is not an additional tax; rather, the U.S. federal income tax liability of persons subject to backup withholding will be reduced by the amount of tax withheld. If withholding results in an overpayment of taxes, a refund or credit may generally be obtained from the IRS, provided that the required information is furnished to the IRS in a timely manner.

Foreign Account Tax Compliance Act (“FATCA”)

The Foreign Account Tax Compliance Act, Treasury Regulations issued thereunder and official IRS guidance, collectively “FATCA,” generally impose a U.S. federal withholding tax of 30% on dividends on, and, subject to the discussion of certain proposed Treasury Regulations below, the gross proceeds from a sale or other disposition of our common stock, paid to a “foreign financial institution” (as specially defined under these rules), unless such institution enters into an agreement with the U.S. government to, among other things, withhold on certain payments and to collect and provide to the U.S. tax authorities substantial information regarding the U.S. account holders of such institution (which includes certain equity and debt holders of such institution, as well as certain account holders that are foreign entities with U.S. owners) or otherwise establishes an exemption. FATCA also generally imposes a U.S. federal withholding tax of 30% on dividends on and, subject to the discussion of certain proposed Treasury Regulations below, the gross proceeds from a sale or other disposition of our common stock paid to a “non-financial foreign entity” (as specially defined under these rules) unless such entity provides the withholding agent with a certification identifying the substantial direct and indirect U.S. owners of the entity, certifies that it does not have any substantial U.S. owners, or otherwise establishes an exemption. The withholding tax will apply regardless of whether the payment otherwise would be exempt from U.S. nonresident and backup withholding tax, including under the other exemptions described above. Under certain circumstances, a non-U.S. holder might be eligible for refunds or credits of such taxes. An intergovernmental agreement between the United States and an applicable foreign country may modify the requirements described in this section. Prospective investors should consult with their own tax advisors regarding the application of FATCA withholding to their investment in, and ownership and disposition of, our common stock.

The Treasury Secretary has issued proposed Treasury Regulations, which, if finalized in their present form, would eliminate withholding under FATCA with respect to payment of gross proceeds from a sale or other disposition of our common stock. In its preamble to such proposed Treasury Regulations, the U.S. Treasury stated that taxpayers may generally rely on the proposed Treasury Regulations until final regulations are issued.

The preceding discussion of U.S. federal tax considerations is for general information only. It is not tax advice to investors in their particular circumstances. Each prospective investor should consult its own tax advisor regarding the particular U.S. federal, state and local and non-U.S. tax consequences of purchasing, holding and disposing of our common stock, including the consequences of any proposed change in applicable laws.

UNDERWRITING

We and the underwriters named below have entered into an underwriting agreement with respect to the shares being offered. Subject to certain conditions, each underwriter has severally agreed to purchase the number of shares indicated in the following table. Goldman Sachs & Co. LLC and J.P. Morgan Securities LLC are the representatives of the underwriters.

Underwriters	Number of Shares
Goldman Sachs & Co. LLC	
J.P. Morgan Securities LLC	
Jefferies LLC	
Berenberg Capital Markets LLC	
Cantor Fitzgerald & Co.	
H.C. Wainwright & Co., LLC	
Total	

The underwriters will be committed to take and pay for all of the shares being offered, if any are taken, other than the shares covered by the option described below unless and until this option is exercised.

The underwriters will have an option to buy up to approximately _____ additional shares from us to cover sales by the underwriters of a greater number of shares than the total number set forth in the table above. They may exercise that option for 30 days. If any shares are purchased pursuant to this option, the underwriters will severally purchase shares in approximately the same proportion as set forth in the table above.

The following table shows the per share and total underwriting discounts and commissions to be paid to the underwriters by us. Such amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase additional shares.

Paid by the Company	No Exercise	Full Exercise
Per Share	\$	\$
Total	\$	\$

Shares sold by the underwriters to the public will be offered at the public offering price set forth on the cover of this prospectus. Any shares sold by the underwriters to securities dealers may be sold at a discount of up to \$ _____ per share from the public offering price. After the initial offering of the shares, the representatives may change the offering price and the other selling terms. The offering of the shares by the underwriters is subject to receipt and acceptance and subject to the underwriters' right to reject any order in whole or in part.

We have agreed that, without the prior written consent of the representatives, for a period of 90 days after the date of this prospectus supplement, we will not (1) offer, sell, contract to sell, pledge, grant any option to purchase, make any short sale or otherwise transfer or dispose of, directly or indirectly, or file with or confidentially submit to the SEC a registration statement under the Securities Act relating to any of our securities that are substantially similar to our common stock, including but not limited to any options or warrants to purchase shares of our common stock or any securities that are convertible into or exchangeable for, or that represent the right to receive common stock or any such substantially similar securities, or publicly disclose the intention to make any offer, sale, pledge, disposition or filing, or (2) enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of our common stock or other securities, whether any such transaction described in clause (1) or (2) above is to be settled by delivery of our common stock or other securities, in cash or otherwise. This agreement does not apply to (a) the shares to be sold in this offering, (b) shares issued upon the exercise or settlement of options pursuant to our equity incentive plans or upon the conversion of outstanding convertible securities as described in the Pricing Prospectus, (c) shares of our common stock or securities convertible into, exchangeable for or that represent the right to receive shares of common stock, in each case pursuant to our equity incentive plans, (d) shares of our common stock or securities convertible into, exchangeable for or that represent the right to receive shares of common stock in connection with (1) our acquisition of the business, technology, not less than a majority or controlling portion of the securities, property or other assets of another person or entity or pursuant to an employee benefit plan assumed by us in connection with such acquisition and the issuance of any such securities pursuant to any such agreement, or (2) bona fide commercial transactions (including joint ventures, commercial relationships, or other strategic transactions), or (e) the filing of any registration statement on Form S-8 relating to securities granted or to be granted under our equity incentive plans; provided, that the aggregate number of shares that we may sell or issue or agree to sell or issue in connection with a transaction described in clause (d) shall not exceed 7.5% of the total number of shares outstanding immediately following this offering; and provided, further, that each recipient of any securities described in clauses (d) and (e) shall enter into a lock-up agreement.

Our directors and executive officers have entered into lock-up agreements with the representatives prior to the commencement of this offering, pursuant to which each such person or entity, for a period of 45 days after the date of this prospectus supplement (the "restricted period"), may not, without the prior written consent of the representatives, (i) offer, sell, contract to sell, pledge, grant any option to purchase, make any short sale, lend or otherwise dispose of any shares of common stock, or any options or warrants to purchase any shares of common stock, or any securities convertible into, exchangeable for or that represent the right to receive shares of common stock, (ii) engage in any hedging or other transaction or arrangement which is designed to or which reasonably could be expected to lead to or result in a sale, loan, pledge, other disposition or transfer of any of the economic consequences of ownership, in whole or in part, directly or indirectly, of any shares, whether any such transaction or arrangement would be settled by delivery of common stock, other securities or cash, or (iii) otherwise make any public announcement or SEC filing relating to any intention to engage in any of the foregoing transactions, other than any shares sold to the underwriters pursuant to the underwriting agreement.

The restrictions described in the immediately preceding paragraph do not prohibit:

- transfers of shares as a bona fide gift, including without limitation to a charitable organization or educational institution, or for bona fide estate planning purposes;
- transfers to any immediate family member or to a trust or other legal entity for the direct or indirect benefit of the transferor, or the immediate family of the transferor, or if the undersigned is a trust, to a trustor or beneficiary of the trust or to the estate of a beneficiary of such trust, provided that any such transfer shall not involve a disposition for value;
- transfers by will, other testamentary document or the laws of intestate succession;

- transfers in connection with the sale of the transferor's shares acquired in open market transactions on or after the offering;
- transfers from a corporation, partnership, limited liability company, trust or other business entity, (A) to another corporation, member, partner, partnership, limited liability company, trust or other business entity that is an affiliate (as defined in Rule 405 under the Securities Act), or to any investment fund or other entity controlling, controlled by, managing or managed by or under common control with the transferor or affiliates of the transferor, or (B) as part of a distribution, transfer or disposition by the transferor to its or its affiliates' directors, officers, employees, managers, managing members, members, stockholders, partners, beneficiaries (or the estates thereof) or other equity holders;
- (a) the surrender or forfeiture of shares in connection with the "net" or "cashless" exercise or settlement of stock options, other rights to purchase shares or other awards expiring during the restricted period, or for the payment of tax withholdings or remittance payments due as a result of the vesting, settlement, or exercise of such options, rights or other awards, in all such cases pursuant to an equity incentive plan, stock purchase plan or other employee benefit plan, or (b) surrender or forfeiture to us of shares of common stock upon the conversion of a convertible security in order to cover withholding tax obligations in connection with such conversion;
- transfers in connection with a contractual arrangement that provides for the repurchase by us of shares from a service provider in connection with termination of service;
- transfers in connection with the conversion of any convertible security into shares of common stock;
- transfers pursuant to a bona fide third-party tender offer, merger, consolidation or similar transaction that is approved by the board of directors and made to all holders of our capital stock;
- transfers by operation of law, including pursuant to orders of a court, a qualified domestic order or in connection with a divorce settlement; or
- transfers pursuant to a trading plan adopted pursuant to Rule 10b5-1 of the Exchange Act prior to the date of the underwriting agreement.

In connection with the offering, the underwriters may purchase and sell shares of common stock in the open market. These transactions may include short sales, stabilizing transactions and purchases to cover positions created by short sales. Short sales involve the sale by the underwriters of a greater number of shares than they are required to purchase in the offering, and a short position represents the amount of such sales that have not been covered by subsequent purchases. A "covered short position" is a short position that is not greater than the amount of additional shares for which the underwriters' option described above may be exercised. The underwriters may cover any covered short position by either exercising their option to purchase additional shares or purchasing shares in the open market. In determining the source of shares to cover the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase additional shares pursuant to the option described above. "Naked" short sales are any short sales that create a short position greater than the amount of additional shares for which the option described above may be exercised. The underwriters must cover any such naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in the offering. Stabilizing transactions consist of various bids for or purchases of common stock made by the underwriters in the open market prior to the completion of the offering.

The underwriters may also impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it, because the representatives have repurchased shares sold by or for the account of such underwriter in stabilizing or short covering transactions.

Purchases to cover a short position and stabilizing transactions, as well as other purchases by the underwriters for their own accounts, may have the effect of preventing or retarding a decline in the market price of our stock, and together with the imposition of the penalty bid, may stabilize, maintain or otherwise affect the market price of the common stock. As a result, the price of the common stock may be higher than the price that otherwise might exist in the open market. The underwriters are not required to engage in these activities and may end any of these activities at any time. These transactions may be effected on Nasdaq, in the over-the-counter market or otherwise.

Certain of the underwriters and their affiliates have provided in the past to us and our affiliates and may provide from time to time in the future certain commercial banking, financial advisory, investment banking and other services for us and such affiliates in the ordinary course of their business, for which they have received and may continue to receive customary fees and commissions. Goldman Sachs & Co. LLC and Cantor Fitzgerald & Co. are sales agents under our equity distribution agreement dated February 28, 2022 between us and Goldman Sachs & Co. LLC, SVB Securities LLC, and Cantor Fitzgerald & Co. Under the equity distribution agreement, we may offer and sell, from time to time, shares of our common stock through Goldman Sachs & Co. LLC and Cantor Fitzgerald & Co. in an “at the market offering” as defined in Rule 415(a)(4) promulgated under the Securities Act. In addition, from time to time, certain of the underwriters and their affiliates may effect transactions for their own account or the account of customers, and hold on behalf of themselves or their customers, long or short positions in our debt or equity securities or loans, and may do so in the future.

Our common stock is quoted on The Nasdaq Global Select Market (“Nasdaq”) under the symbol “DNLI.”

Selling Restrictions

Other than in the United States, no action has been taken by us or the underwriters that would permit a public offering of the securities offered by this prospectus supplement in any jurisdiction where action for that purpose is required. The securities offered by this prospectus supplement may not be offered or sold, directly or indirectly, nor may this prospectus supplement or any other offering material or advertisements in connection with the offer and sale of any such securities be distributed or published in any jurisdiction, except under circumstances that will result in compliance with the applicable rules and regulations of that jurisdiction. Persons into whose possession this prospectus supplement comes are advised to inform themselves about and to observe any restrictions relating to the offering and the distribution of this prospectus supplement. This prospectus supplement does not constitute an offer to sell or a solicitation of an offer to buy any securities offered by this prospectus in any jurisdiction in which such an offer or a solicitation is unlawful.

European Economic Area

In relation to each Member State of the European Economic Area (each, a Member State), no common shares (the “Shares”) have been offered or will be offered pursuant to the offering to the public in that Member State prior to the publication of a prospectus in relation to the Shares which has been approved by the competent authority in that Member State or, where appropriate, approved in another Member State and notified to the competent authority in that Member State, all in accordance with the Prospectus Regulation), except that offer of Shares may be made to the public in that Member State at any time under the following exemptions under the Prospectus Regulation:

- a. to any legal entity which is a qualified investor as defined under the Prospectus Regulation;

- b. to fewer than 150 natural or legal persons (other than qualified investors as defined under the Prospectus Regulation), subject to obtaining the prior consent of the Representatives for any such offer; or
- c. in any other circumstances falling within Article 1(4) of the Prospectus Regulation,

provided that no such offer of Shares shall require the company or any Representative to publish a prospectus pursuant to Article 3 of the Prospectus Regulation or supplement a prospectus pursuant to Article 23 of Prospectus Regulation and each person who initially acquires any shares or to whom any offer is made will be deemed to have represented, acknowledged and agreed to and with each of the underwriters and us that it is a "qualified investor" within the meaning of Article 2(e) of the Prospectus Regulation. In the case of any shares being offered to a financial intermediary as that term is used in the Prospectus Regulation, each such financial intermediary will be deemed to have represented, acknowledged and agreed that the shares acquired by it in the offer have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in circumstances which may give rise to an offer of any shares to the public other than their offer or resale in a Member State to qualified investors as so defined or in circumstances in which the prior consent of the underwriters have been obtained to each such proposed offer or resale.

For the purposes of this provision, the expression an "offer to the public" in relation to any Shares in any Member State means the communication in any form and by any means of sufficient information on the terms of the offer and any Shares to be offered so as to enable an investor to decide to purchase or subscribe for any Shares, and the expression "Prospectus Regulation" means Regulation (EU) 2017/1129.

United Kingdom

No shares have been offered or will be offered pursuant to the offering to the public in the United Kingdom prior to the publication of a prospectus in relation to the shares which is to be treated as if it had been approved by the Financial Conduct Authority in accordance with the transitional provisions in Article 74 (transitional provisions) of the Prospectus (Amendment etc.) (EU Exit) Regulations 2019/1234, except that the shares may be offered to the public in the United Kingdom at any time:

- (a) to any legal entity which is a qualified investor as defined under Article 2 of the UK Prospectus Regulation;
- (b) to fewer than 150 natural or legal persons (other than qualified investors as defined under Article 2 of the UK Prospectus Regulation), subject to obtaining the prior consent of underwriters for any such offer; or
- (c) in any other circumstances falling within Section 86 of the FSMA.

provided that no such offer of the Shares shall require the issuer or any underwriter to publish a prospectus pursuant to Section 85 of the FSMA or supplement a prospectus pursuant to Article 23 of the UK Prospectus Regulation. For the purposes of this provision, the expression an “offer to the public” in relation to the Shares in the United Kingdom means the communication in any form and by any means of sufficient information on the terms of the offer and any shares to be offered so as to enable an investor to decide to purchase or subscribe for any shares and the expression “UK Prospectus Regulation” means Regulation (EU) 2017/1129 as it forms part of domestic law by virtue of the European Union (Withdrawal) Act 2018.

In addition, in the United Kingdom, this document is being distributed only to, and is directed only at, and any offer subsequently made may only be directed at persons who are “qualified investors” (as defined in the Prospectus Regulation) (i) who have professional experience in matters relating to investments falling within Article 19(5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended (the “Order”) and/or (ii) who are high net worth companies (or persons to whom it may otherwise be lawfully communicated) falling within Article 49(2)(a) to (d) of the Order (all such persons together being referred to as “relevant persons”) or otherwise in circumstances which have not resulted and will not result in an offer to the public of the shares in the United Kingdom within the meaning of the Financial Services and Markets Act 2000.

Any person in the United Kingdom that is not a relevant person should not act or rely on the information included in this document or use it as basis for taking any action. In the United Kingdom, any investment or investment activity that this document relates to may be made or taken exclusively by relevant persons.

Canada

The common stock may be sold in Canada only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of the Securities Act (Ontario), and are permitted clients, as defined in National Instrument 31-103 Registration Requirements, Exemptions, and Ongoing Registrant Obligations. Any resale of the common stock must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser’s province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser’s province or territory of these rights or consult with a legal advisor.

Pursuant to section 3A.3 of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

Hong Kong

The contents of this prospectus supplement and the accompanying prospectus have not been reviewed by any regulatory authority in Hong Kong. You are advised to exercise caution in relation to the offer. If you are in any doubt about any of the contents of this prospectus supplement or the accompanying prospectus, you should obtain independent professional advice. Please note that (i) our common stock may not be offered or sold in Hong Kong by means of this prospectus supplement or the accompanying prospectus or any document other than to “professional investors” within the meaning of Part I of Schedule 1 of the Securities and Futures Ordinance (Cap.571, Laws of Hong Kong) (SFO) and any rules made thereunder, or in other circumstances which do not result in the document being a “prospectus” within the meaning of the Companies Ordinance (Cap.32, Laws of Hong Kong) (CO) or which do not constitute an offer or invitation to the public for the purpose of the CO or the SFO, and (ii) no advertisement, invitation or document relating to our securities may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong (except if permitted to do so under the securities laws of Hong Kong) other than with respect to the securities which are or are intended to be disposed of only to persons outside Hong Kong or only to “professional investors” within the meaning of the SFO and any rules made thereunder.

Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the common stock may not be circulated or distributed, nor may the common stock be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor (as defined under Section 4A of the Securities and Futures Act, Chapter 289 of Singapore, or the SFA, under Section 274 of the SFA, (ii) to a relevant person (as defined in Section 275(2) of the SFA) pursuant to Section 275(1) of the SFA, or any person pursuant to Section 275(1A) of the SFA, and in accordance with the conditions specified in Section 275 of the SFA or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA, in each case subject to conditions set forth in the SFA.

Where the shares are subscribed or purchased under Section 275 of the SFA by a relevant person which is (i) a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor, or (ii) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary of the trust is an individual who is an accredited investor, securities or securities-based derivatives contracts (each term as defined in Section 2(1) of the SFA) of that corporation or the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferred within six months after that corporation or that trust has acquired the shares pursuant to an offer made under Section 275 of the SFA except (a) to an institutional investor or to a relevant person, or to any person arising from an offer referred to in Section 275(1A) or Section 276(4)(i)(B) of the SFA; (b) where no consideration is or will be given for the transfer; (c) where the transfer is by operation of law; (d) as specified in Section 276(7) of the SFA; or (e) as specified in Regulation 37A of the Securities and Futures (Offers of Investments) (Securities and Securities-based Derivatives Contracts) Regulations 2018.

In connection with Section 309B of the SFA and the Capital Markets Products (the “CMP”) Regulations 2018, the shares are prescribed capital markets products (as defined in the CMP Regulations 2018) and Excluded Investment Products (as defined in Monetary Authority of Singapore Notice SFA 04-N12: Notice on the Sale of Investment Products and Monetary Authority of Singapore Notice FAA-N16: Notice on Recommendations on Investment Products).

Japan

The common stock has not been and will not be registered under the Financial Instruments and Exchange Act of Japan (Act No. 25 of 1948, as amended), or the FIEA. The common stock may not be offered or sold, directly or indirectly, in Japan or to or for the benefit of any resident of Japan (including any person resident in Japan or any corporation or other entity organized under the laws of Japan) or to others for reoffering or resale, directly or indirectly, in Japan or to or for the benefit of any resident of Japan, except pursuant to an exemption from the registration requirements of the FIEA and otherwise in compliance with any relevant laws and regulations of Japan.

We estimate that our share of the total expenses of the offering, excluding underwriting discounts and commissions, will be approximately . We will agree to reimburse the underwriters for expenses related to any applicable state securities filings and to the Financial Industry Regulatory Authority incurred by them in connection with this offering in an amount up to \$10,000.

We will agree to indemnify the several underwriters against certain liabilities, including liabilities under the Securities Act.

The underwriters and their respective affiliates are full service financial institutions engaged in various activities, which may include sales and trading, commercial and investment banking, advisory, investment management, investment research, principal investment, hedging, market making, brokerage and other financial and non-financial activities and services. Certain of the underwriters and their respective affiliates have provided, and may in the future provide, a variety of these services to the issuer and to persons and entities with relationships with the issuer, for which they received or will receive customary fees and expenses.

In the ordinary course of their various business activities, the underwriters and their respective affiliates, officers, directors and employees may purchase, sell or hold a broad array of investments and actively trade securities, derivatives, loans, commodities, currencies, credit default swaps and other financial instruments for their own account and for the accounts of their customers, and such investment and trading activities may involve or relate to assets, securities and/or instruments of the issuer (directly, as collateral securing other obligations or otherwise) and/or persons and entities with relationships with the issuer. The underwriters and their respective affiliates may also communicate independent investment recommendations, market color or trading ideas and/or publish or express independent research views in respect of such assets, securities or instruments and may at any time hold, or recommend to clients that they should acquire, long and/or short positions in such assets, securities and instruments.

LEGAL MATTERS

The validity of the issuance of our common stock offered in this prospectus supplement will be passed upon for us by Wilson Sonsini Goodrich & Rosati, Professional Corporation, Palo Alto, California. Davis Polk & Wardwell LLP, Menlo Park, California, is acting as counsel for the underwriters.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2021, and the effectiveness of our internal control over financial reporting as of December 31, 2021, as set forth in their reports, which are incorporated by reference in this prospectus supplement and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's reports, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND ADDITIONAL INFORMATION

We have filed with the SEC a registration statement on Form S-3 under the Securities Act of 1933, as amended, or the Securities Act, with respect to the common stock offered by this prospectus supplement. This prospectus supplement, filed as part of the registration statement, does not contain all the information set forth in the registration statement and its exhibits and schedules, portions of which have been omitted as permitted by the rules and regulations of the SEC. For further information about us, we refer you to the registration statement and to its exhibits and schedules.

We file annual, quarterly and current reports, proxy statements and other information with the SEC. You may read and copy any materials we file at the SEC's Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549. Please call the SEC at 1-800-SEC-0330 for further information about the Public Reference Room. The SEC also maintains a website at www.sec.gov that contains periodic and current reports, proxy and information statements, and other information regarding registrants that are filed electronically with the SEC.

These documents are also available, free of charge, through the Investors section of our website, which is located at www.denalitherapeutics.com. Information contained on our website is not incorporated by reference into this prospectus supplement or the accompanying prospectus and you should not consider information on our website to be part of this prospectus supplement or the accompanying prospectus.

INCORPORATION BY REFERENCE

The SEC allows us to incorporate by reference much of the information we file with the SEC, which means that we can disclose important information to you by referring you to those publicly available documents. The information that we incorporate by reference in this prospectus supplement and the accompanying prospectus is considered to be part of this prospectus. Because we are incorporating by reference future filings with the SEC, this prospectus supplement is continually updated and those future filings may modify or supersede some of the information included or incorporated in this prospectus supplement. This means that you must look at all of the SEC filings that we incorporate by reference to determine if any of the statements in this prospectus supplement, the accompanying prospectus or in any document previously incorporated by reference have been modified or superseded. This prospectus supplement incorporates by reference the documents listed below (File No. 001-35966) and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act (in each case, other than those documents or the portions of those documents not deemed to be filed) between the date of this prospectus supplement and the termination of this offering:

- Annual Report on [Form 10-K](#) for the year ended December 31, 2021, as filed with the SEC on February 28, 2022;
- The information specifically incorporated by reference into our Annual Report on Form 10-K for the year ended December 31, 2021 from our definitive proxy statement on [Schedule 14A](#) (other than information furnished rather than filed), which was filed with the SEC on April 19, 2022;
- Quarterly Reports on Form 10-Q for the fiscal quarters ended March 31, 2022 and June 30, 2022, as filed with the SEC on [May 5, 2022](#), and [August 8, 2022](#), respectively;
- Current Reports on Form 8-K filed with the SEC on [February 28, 2022 \(Item 1.01\)](#), [March 16, 2022](#) and [June 3, 2022](#); and
- The description of our common stock contained in our registration statement on [Form 8-A](#), which was filed with the SEC on November 30, 2017, including any amendment or report filed for the purpose of updating such description.

You may request a copy of these filings, at no cost, by contacting us, either orally or in writing, at the following:

Denali Therapeutics Inc.

161 Oyster Point Blvd.

South San Francisco CA 94080

Phone: (650) 866-8548

PROSPECTUS

DENALI THERAPEUTICS INC.



Common Stock
Preferred Stock
Debt Securities
Warrants
Purchase Contracts
Units

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

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

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

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

Our common stock is listed on The Nasdaq Global Select Market ("Nasdaq") under the symbol "DNLI." On February 25, 2022, the last reported sale price of our common stock on Nasdaq was \$33.03 per share.

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

The date of this prospectus is February 28, 2022.

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ABOUT THIS PROSPECTUS

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

We have not authorized anyone to provide you with any information or to make any representations other than those contained or incorporated by reference in this prospectus, any applicable prospectus supplement or any free writing prospectuses prepared by or on behalf of us or to which we have referred you. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. We will not make an offer to sell these securities in any jurisdiction where the offer or sale is not permitted. You should assume that the information appearing in this prospectus and the applicable prospectus supplement to this prospectus is accurate as of the date on its respective cover or as otherwise specified therein and that any information incorporated by reference is accurate only as of the date of the document incorporated by reference, unless we indicate otherwise. Our business, financial condition, results of operations and prospects may have changed since those dates. This prospectus incorporates by reference, and any prospectus supplement or free writing prospectus may contain and incorporate by reference, market data and industry statistics and forecasts that are based on independent industry publications and other publicly available information. Although we believe these sources are reliable, we do not guarantee the accuracy or completeness of this information and we have not independently verified this information. Although we are not aware of any misstatements regarding the market and industry data presented in this prospectus, the applicable prospectus supplement and the documents incorporated herein and therein by reference, these estimates involve risks and uncertainties and are subject to change based on various factors, including those discussed under the heading "Risk Factors" contained or incorporated by reference in this prospectus, the applicable prospectus supplement and any related free writing prospectus and under similar headings in other documents that are incorporated by reference into this prospectus. Accordingly, investors should not place undue reliance on this information.

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

THE COMPANY

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

We were incorporated in the State of Delaware in 2013. Our principal executive offices are located at 161 Oyster Point Blvd., South San Francisco, California 94080. Our telephone number is (650) 866-8548. Our website address is www.denalitherapeutics.com. The information on our web site, or that can be accessed through our web site, however, is not, and should not be deemed to be, a part of this prospectus. We also use our website as a means of disclosing material non-public information and for complying with our disclosure obligations under Regulation FD.

RISK FACTORS

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

USE OF PROCEEDS

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

DESCRIPTION OF SECURITIES

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

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

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

PLAN OF DISTRIBUTION

We may sell the offered securities from time to time:

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

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

LEGAL MATTERS

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

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2021, and the effectiveness of our internal control over financial reporting as of December 31, 2021, as set forth in their reports, which are incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's reports, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

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

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

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

INCORPORATION BY REFERENCE

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

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

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

- Our Annual Report on [Form 10-K](#) for the fiscal year ended December 31, 2021 filed on February 28, 2022.
- The description of our common stock, par value \$0.01 per share, contained in our registration statement on [Form 8-A](#), filed with the SEC on November 30, 2017, including any subsequent filed amendments and reports updating such description.

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

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

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

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

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

DENALI THERAPEUTICS INC.



Common Stock

Preferred Stock

Debt Securities

Warrants

Purchase Contracts

Units
