UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2020

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

For the transition period from _____ to _____

Commission File No. 001-37627

WAVE LIFE SCIENCES LTD.

(Exact name of registrant as specified in its charter)

Singapore	**Not applicable**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
7 Straits View #12-00, Marina One East Tower Singapore	**018936**
(Address of principal executive offices)	**(Zip code)**

Registrant's telephone number, including area code: +65 6236 3388

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

Title of each class	Trading symbol	Name of each exchange on which registered
$0 Par Value Ordinary Shares	WVE	The Nasdaq Global Market

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

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

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

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

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

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

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

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

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

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

The aggregate market value of the registrant's voting and non-voting ordinary shares held by non-affiliates of the registrant (without admitting that any person whose shares are not included in such calculation is an affiliate) computed by reference to the price at which the ordinary shares were last sold as of the last business day of the registrant's most recently completed second fiscal quarter (June 30, 2020) was $267,103,358. The number of outstanding ordinary shares of the registrant as of February 22, 2021 was 48,997,368.

DOCUMENTS INCORPORATED BY REFERENCE

If the Registrant's Definitive Proxy Statement relating to the 2021 Annual General Meeting of Shareholders (the "Proxy Statement") is filed with the Commission within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K, then portions of the Proxy Statement will be incorporated by reference into Part III of this Annual Report on Form 10-K. If the Proxy Statement is not filed within such 120-day period, then the Registrant will file an amendment to this Annual Report within such 120-day period that will contain the information required to be included or incorporated by reference into Part III of this Annual Report.

WAVE LIFE SCIENCES LTD.

ANNUAL REPORT ON FORM 10-K

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Special Note Regarding Forward-Looking Statements

This Annual Report on Form 10-K contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the "Securities Act"), and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), that relate to future events or to our future operations or financial performance. Any forward-looking statement involves known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to differ materially from any future results, levels of activity, performance or achievements expressed or implied by such forward-looking statement. In some cases, forward-looking statements are identified by the words "anticipate," "believe," "continue," "could," "estimate," "expect," "future," "goals," "intend," "likely," "may," "might," "ongoing," "objective," "plan," "potential," "predict," "project," "seek," "should," "strategy," "target," "will" and "would" or the negative of these terms, or other comparable terminology intended to identify statements about the future, although not all forward-looking statements contain these identifying words. Forward-looking statements include statements, other than statements of historical fact, about, among other things: our ability to fund our future operations; our financial position, revenues, costs, expenses, uses of cash and capital requirements; our need for additional financing or the period for which our existing cash resources will be sufficient to meet our operating requirements; the success, progress, number, scope, cost, duration, timing or results of our research and development activities, preclinical studies and clinical trials, including the timing for initiation or completion of or availability of results from any preclinical studies and clinical trials or for submission, review or approval of any regulatory filing; the timing of, and our ability to, obtain and maintain regulatory approvals for any of our product candidates; the potential benefits that may be derived from any of our product candidates; our strategies, prospects, plans, goals, expectations, forecasts or objectives; the success of our collaborations with third parties; any payment that our collaboration partners may make to us; our ability to identify and develop new product candidates; our intellectual property position; our commercialization, marketing and manufacturing capabilities and strategy; our ability to develop sales and marketing capabilities; our estimates regarding future expenses and needs for additional financing; our ability to identify, recruit and retain key personnel; our financial performance; developments and projections relating to our competitors in the industry; our liquidity and working capital requirements; the expected impact of new accounting standards; and our expectations regarding the impact of COVID-19 and variants thereof, on our research and development activities, preclinical studies and clinical trials, supply of drug product, and our workforce.

Although we believe that we have a reasonable basis for each forward-looking statement contained in this report, we caution you that these statements are based on our estimates or projections of the future that are subject to known and unknown risks and uncertainties and other important factors that may cause our actual results, level of activity, performance or achievements expressed or implied by any forward-looking statement to differ. These risks, uncertainties and other factors include, among other things, our critical accounting policies and: the ability of our preclinical studies to produce data sufficient to support the filing of global clinical trial applications and the timing thereof; our ability to continue to build and maintain the company infrastructure and personnel needed to achieve our goals; the clinical results and timing of our programs, which may not support further development of our product candidates; actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials; our effectiveness in managing current and future clinical trials and regulatory processes; the success of our platform in identifying viable candidates; the continued development and acceptance of nucleic acid therapeutics as a class of drugs; our ability to demonstrate the therapeutic benefits of our stereopure candidates in clinical trials, including our ability to develop candidates across multiple therapeutic modalities; our ability to obtain, maintain and protect intellectual property; our ability to enforce our patents against infringers and defend our patent portfolio against challenges from third parties; our ability to fund our operations and to raise additional capital as needed; competition from others developing therapies for similar uses; the severity and duration of the COVID-19 pandemic; and the COVID-19 pandemic and variants thereof, may negatively impact the conduct of, and the timing of enrollment, completion and reporting with respect to, our clinical trials; any other impacts on our business as a result of or related to the COVID-19 pandemic, as well as other risks and uncertainties under the "Risk Factors" section of this Annual Report on Form 10-K and in other filings we make with the Securities and Exchange Commission.

Each forward-looking statement contained in this report is based on a combination of facts and factors currently known by us and our expectations of the future, about which we cannot be certain.

As a result of these factors, we cannot assure you that the forward-looking statements in this Annual Report on Form 10-K will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, these statements should not be regarded as representations or warranties by us or any other person that we will achieve our objectives and plans in any specified timeframe, or at all. We caution you not to place undue reliance on any forward-looking statement.

In addition, any forward-looking statement in this report represents our views only as of the date of this report and should not be relied upon as representing our views as of any subsequent date. We anticipate that subsequent events and developments may cause our views to change. Although we may elect to update these forward-looking statements publicly at some point in the future, we undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by applicable law. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

As used in this Annual Report on Form 10-K, unless otherwise stated or the context otherwise indicates, references to “Wave,” the “Company,” “we,” “our,” “us” or similar terms refer to Wave Life Sciences Ltd. and our wholly-owned subsidiaries.

The Wave Life Sciences Ltd. and Wave Life Sciences Pte. Ltd. names, the Wave Life Sciences mark, PRISM and the other registered and pending trademarks, trade names and service marks of Wave Life Sciences Ltd. appearing in this Annual Report on Form 10-K are the property of Wave Life Sciences Ltd. This Annual Report on Form 10-K also contains additional trade names, trademarks and service marks belonging to Wave Life Sciences Ltd. and to other companies. We do not intend our use or display of other parties’ trademarks, trade names or service marks to imply, and such use or display should not be construed to imply, a relationship with, or endorsement or sponsorship of us by, these other parties. Solely for convenience, the trademarks and trade names in this Annual Report on Form 10-K are referred to without the ® and ™ symbols, but such reference should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto.

Summary of Risk Factors

We are providing the following summary of the risk factors contained in this Annual Report on Form 10-K to enhance the readability and accessibility of our risk factor disclosures. We encourage you to carefully review the full risk factors contained in this Annual Report on Form 10-K in their entirety for additional information regarding the material factors that make an investment in our securities speculative or risky. These risks and uncertainties include, but are not limited to, the following:

- We are company with a history of losses, and we expect to continue to incur losses for the foreseeable future, and we may never achieve or maintain profitability.
- We will require substantial additional funding, which may not be available on acceptable terms, or at all.
- Our management may not effectively use the proceeds received from sales of our securities and our collaboration partners.
- Our short operating history may make it difficult for shareholders to evaluate the success of our business to date and to assess our future viability.
- We, or third parties upon whom we depend, may face risks related to health epidemics, including the novel coronavirus (COVID-19) pandemic, which may cause adverse effects on our business and operations.
- The approach we are taking to discover and develop oligonucleotides is novel and may never lead to marketable products and there is increased risk that the outcome of our clinical trials will not be sufficient to obtain regulatory approval.
- We may not be able to conduct preclinical studies and/or clinical trials successfully, which could materially harm our business.
- If we cannot successfully manufacture our product candidates for our research and development and preclinical activities, or manufacture sufficient amounts of our product candidates to meet our clinical requirements and timelines, our business may be materially harmed.
- Results of preclinical studies and early clinical trials may not be predictive of results of future clinical trials.
- If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.
- We may be unable to obtain regulatory approval in the United States or foreign jurisdictions and, as a result, be unable to commercialize our product candidates and our ability to generate revenue will be materially impaired.
- If we fail to comply with continuing U.S. and foreign requirements, our regulatory approvals, if obtained, could be limited or withdrawn, we could be subject to other penalties, and our business would be seriously harmed.
- If we are unable to compete effectively with existing drugs, new treatment methods and new technologies, we may be unable to successfully commercialize any drugs that we develop.
- Risks associated with our operations outside of the United States and developments in international trade by the U.S. and foreign governments could adversely affect our business.
- We may not be able to execute our business strategy optimally if we are unable to maintain our existing collaborations or enter into new collaborations with partners that can provide sales, marketing and distribution capabilities and funds for the development and commercialization of our product candidates.
- We rely, and expect to continue to rely, on third parties to conduct some aspects of our compound formulation, research, preclinical studies and clinical trials, and those third parties may not perform satisfactorily, which may harm our business.

- If any of our product candidates are approved for marketing and commercialization and we are unable to develop sales, marketing and distribution capabilities on our own, or enter into agreements with third parties to perform these functions on acceptable terms, we will be unable to commercialize successfully any such future products.
- If we are unable to attract and retain qualified key management and scientists, staff, consultants and advisors, our ability to implement our business plan may be adversely affected.
- If we are not able to obtain and enforce market exclusivity for our technologies or product candidates, development and commercialization of our product candidates may be adversely affected.
- We license patent rights from third-party owners or licensees. If such owners or licensees do not properly or successfully obtain, maintain or enforce the patents underlying such licenses, or if they retain or license to others any competing rights, our competitive position and business prospects may be adversely affected.
- Other companies or organizations may challenge our or our licensors' patent rights or may assert patent rights that prevent us from developing and commercializing our products.
- Intellectual property rights of third parties could adversely affect our ability to commercialize our product candidates, and we might be required to litigate or obtain licenses from third parties in order to develop or market our product candidates. Such litigation or licenses could be costly or not available on commercially reasonable terms.
- We are incorporated in Singapore and our shareholders may have more difficulty in protecting their interests than they would as shareholders of a corporation incorporated in the United States.
- We are subject to the laws of Singapore, which differ in certain material respects from the laws of the United States. The public market may not be liquid enough for our shareholders to sell their ordinary shares quickly or at market price, or at all.
- The market price of our ordinary shares is likely to be highly volatile due to various/numerous factors, which could cause the price of our ordinary shares to decline and we may incur significant costs from class action litigation due to share volatility.

PART I

Item 1. Business

Overview

We are a clinical-stage genetic medicines company committed to delivering life-changing treatments for people battling devastating diseases. Using PRISM™, our proprietary discovery and drug development platform that enables the precise design, optimization and production of novel stereopure oligonucleotides, we aspire to develop best in class medicines for genetically defined diseases with a high degree of unmet need.

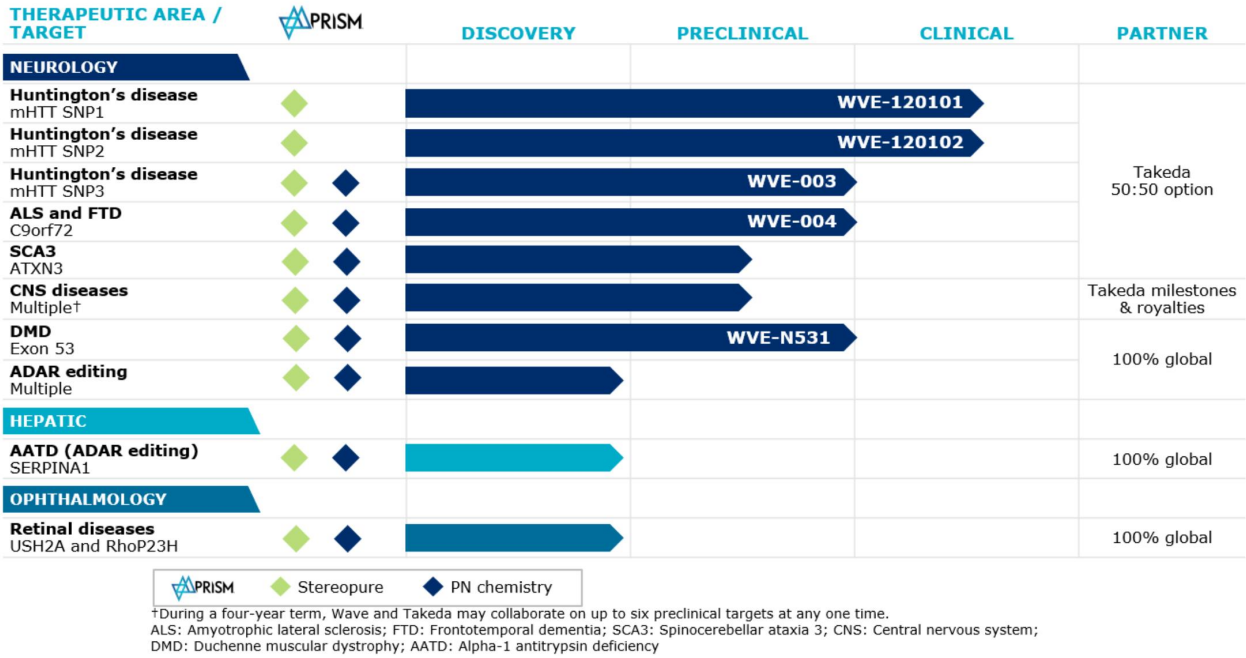
We are developing oligonucleotides that target ribonucleic acid ("RNA") to either reduce the expression of disease-promoting proteins or transform the production of dysfunctional mutant proteins into the production of functional proteins. By intervening at the RNA level, we have the potential to address diseases that have historically been difficult to treat with small molecules or biologics, while retaining the ability to titrate dose and avoid permanent off-target genetic changes and other challenges associated with DNA editing or gene therapy approaches. The mechanisms that we are currently using to target RNA with our oligonucleotides include silencing, splicing, and ADAR (adenosine deaminases acting on RNA)-mediated RNA editing ("ADAR editing"). Oligonucleotides have additional advantages as a therapeutic class including the ability to access multiple tissue types and the ability to modulate the frequency of dosing to ensure broad distribution within tissues over time. Oligonucleotides also have well-established manufacturing processes and validated test methods based on decades of improvements.

The oligonucleotides we are developing with PRISM are stereopure and differ from the mixture-based oligonucleotides currently on the market or in development by others. A stereopure oligonucleotide is comprised of molecules with atoms precisely arranged in three-dimensional orientations at each linkage. Based on our preclinical studies, we believe that controlling the stereochemistry of each backbone position will allow us to optimize the pharmacological profile of our oligonucleotides by maximizing the potential therapeutic benefit while minimizing the potential for side effects and safety risks. To further mitigate pharmacological risks and potential manufacturing challenges, our approach focuses on designing oligonucleotides without the need for delivery vehicles. Through our work in developing stereopure oligonucleotides, we have created and continue to evolve PRISM, our proprietary discovery and drug development platform.

PRISM enables us to target genetically defined diseases with stereopure oligonucleotides across multiple therapeutic modalities. PRISM combines our unique ability to construct stereopure oligonucleotides with a deep understanding of how the interplay among oligonucleotide sequence, chemistry and backbone stereochemistry impacts key pharmacological properties. By exploring these interactions through iterative analysis of *in vitro* and *in vivo* outcomes and machine learning-driven predictive modeling, we continue to define design principles that we deploy across programs to rapidly develop and manufacture clinical candidates that meet pre-defined product profiles. In August 2020, we introduced our novel PN backbone chemistry modifications, which were discovered through PRISM and have been shown preclinically to increase potency, tissue exposure and durability across various modalities.

Our lead clinical development programs are focused on genetic diseases within neurology. Our first stereopure therapeutic candidates in development, WVE-120101 and WVE-120102, are designed to selectively target mutant huntingtin ("mHTT") and spare wild-type, or healthy, huntingtin ("wtHTT") for the treatment of Huntington's disease ("HD"). WVE-120101 and WVE-120102 are currently being studied in two Phase 1b/2a clinical trials, PRECISION-HD1 and PRECISION-HD2, and we expect to deliver data from both trials at the end of the first quarter of 2021. We also expect to initiate dosing in three new clinical trials with compounds containing our novel PN backbone chemistry modifications in 2021. These new programs include WVE-003, our mHTT SNP3 program for the treatment of HD, WVE-004, our C9orf72 program for the treatment of amyotrophic lateral sclerosis ("ALS") and frontotemporal dementia ("FTD"), and WVE-N531, our Exon 53 program for the treatment of Duchenne muscular dystrophy ("DMD"). We continue to advance our ATXN3 program in SCA3. We are also pursuing additional programs in disorders of the central nervous system ("CNS"), including Alzheimer's disease, Parkinson's disease, and others, in collaboration with Takeda Pharmaceutical Company Limited ("Takeda"). In addition to neurology, our pipeline includes programs in hepatic diseases, including alpha-1 antitrypsin disease ("AATD"), and ophthalmologic disorders, specifically inherited retinal diseases. We continue to invest in PRISM to continue to evolve and apply the expanding capabilities and promise of our unique platform. We have also established and continue to enhance our internal current good manufacturing practices ("cGMP") manufacturing capabilities to increase control and visibility of our drug substance supply chain, while continuing to innovate oligonucleotide manufacturing.

Our Current Programs



Additional details regarding our programs are set forth below.

Neurology

Huntington's Disease ("HD"): HD is a rare hereditary neurodegenerative disease that results in early death and for which there is no cure. HD is caused by a mutation (i.e., an expanded CAG triplet repeat) in the HTT gene, which results in production of mutant HTT ("mHTT") protein. In HD patients, there is a progressive loss of neurons in the brain leading to cognitive, psychiatric and motor disabilities. HD patients still possess wild-type (healthy) HTT ("wtHTT") protein, which is important for neuronal function, and there is increasing evidence that wtHTT may be neuroprotective in an adult brain. Additionally, a dominant gain of function in mHTT protein and a concurrent loss of function of wtHTT protein may be important components of the pathophysiology of HD. Accordingly, suppression of wtHTT may have detrimental long-term consequences. A 2020 *Nature* publication (Poplawski, G.H.D., et al. Injured adult neurons regress to an embryonic transcriptional growth state. *Nature* 581, 77–82 (2020)) described results that involved conditional knockout of huntingtin in 4-month old mice (post-neuronal development), which demonstrated that huntingtin is at the center of the regeneration transcriptome and played an essential role in neural plasticity. In October 2019, at our Analyst and Investor Research Day, key opinion leaders in HD research presented data suggesting that wtHTT is neuroprotective in an adult brain; transport of key neurotrophic factors such as brain-derived neurotrophic factor ("BDNF") are regulated by wtHTT levels; and HD may be caused by a dominant gain of function in mHTT and a loss of function of wtHTT protein. Further, the relative proportion of wtHTT to mHTT is critical based on evidence that suggests increased amount of wtHTT relative to mHTT may result in slower disease progression (measured by age-at-onset). Also, HD patients that lack wtHTT all together have significantly more severe disease, as measured by disease progression after symptom onset.

Our HD Portfolio: In HD, we are currently advancing three clinical programs. WVE-120101 and WVE-120102 are our first clinical programs in HD, where each is a distinct stereopure antisense oligonucleotide designed to selectively target a single nucleotide polymorphism ("SNP") associated with the disease-causing mutant huntingtin (mHTT) mRNA transcript within the *HTT* gene: rs362307 ("mHTT SNP1") and rs362331 ("mHTT SNP2"), respectively. Our third program in HD, WVE-003, is also a stereopure antisense oligonucleotide designed to target an undisclosed SNP3, "mHTT SNP3." WVE-003 incorporates our novel PN backbone chemistry modifications, as well as learnings from the first two HD programs. We initiated clinical development of WVE-003 with the submission of a clinical trial application ("CTA") in December 2020. Approximately 50% of the HD population carries SNP1 or SNP2, and, with overlap, up to 70% of the HD population carries SNP1, SNP2 or both. Approximately 40% of the HD population carries SNP3, and, with overlap, up to 80% of the HD population carries at least one of SNP1, SNP2 and/or SNP3. Targeting mRNAs

with these SNPs allows us to lower expression of transcript from the mutant allele, while leaving the healthy transcript relatively intact. The healthy transcript is required to produce wtHTT protein which is important for neuronal function. We commonly refer to this method (or approach) as "allele-selective targeting." SNPs are naturally occurring variations within a given genetic sequence and in certain instances can be used to distinguish between two related copies of a gene where only one is associated with the expression of a disease-causing protein. Our allele-selective approach may also enable us to address the pre-manifest, or asymptomatic, HD patient population in the future. We have shown that by targeting mHTT SNP1 and mHTT SNP2 in preclinical *in vitro* studies, the production of disease-causing proteins associated with HD can be selectively reduced. In addition, we have shown that by targeting mHTT SNP3 in preclinical *in vitro* studies, WVE-003 selectively reduces the expression of mHTT, and by targeting mHTT SNP3 in preclinical *in vivo* studies, WVE-003 demonstrated durable and potent knockdown of mHTT mRNA.

Phase 1b/2a Clinical Trials: PRECISION-HD is a global clinical program consisting of the PRECISION-HD1 and PRECISION-HD2 clinical trials. PRECISION-HD1 and PRECISION-HD2 are two parallel, multicenter, double-blind, randomized, placebo-controlled Phase 1b/2a clinical trials evaluating WVE-120101 and WVE-120102, respectively, administered intrathecally, consisting of single-ascending dose and multiple-ascending dose portions. The primary objective of these two trials is to assess the safety and tolerability of intrathecal doses of WVE-120101 and WVE-120102, respectively, in early manifest HD patients. Additional objectives include measurement of total HTT protein and mHTT protein, and exploratory pharmacokinetic, pharmacodynamic, clinical and MRI endpoints. Each trial is designed with five multi-dose cohorts (2, 4, 8, 16, and 32 mg), each with 12 patients that have Stage I or Stage II HD, ages 25-65, who have screened positively for the presence of SNP1 or SNP2. Outside of the United States, we are conducting both the single-ascending dose and multiple-ascending dose portions of the PRECISION-HD1 and PRECISION-HD2 trials. In the United States, we received approvals to proceed with the single-dose portions of both trials. However, the FDA indicated to us that we cannot progress to the multiple-ascending dose portions of these trials in the United States unless we conduct an additional preclinical study and present the resulting data to the FDA for its review. For the single-dose portion of the PRECISION-HD1 trial in the United States, escalation to our highest proposed doses is subject to the FDA's review and approval of additional monitoring plans. WVE-120101 and WVE-120102 have been granted orphan drug designation for the treatment of HD by the FDA.

PRECISION-HD2 trial: In December 2019, we announced initial clinical data from the ongoing PRECISION-HD2 trial. In an analysis comparing all patients treated with multiple intrathecal doses of WVE-120102 to placebo, a statistically significant reduction of 12.4% ($p<0.05$) in mHTT protein was observed in cerebrospinal fluid ("CSF"). An analysis to assess a dose response across treatment groups (2, 4, 8, or 16 mg) suggested a statistically significant response in mHTT reduction at the highest doses tested ($p=0.03$). WVE-120102 was generally safe and well tolerated across all cohorts. These topline data supported the addition of higher dose cohorts, and a 32 mg cohort was initiated in January 2020, which is fully enrolled. We expect to report biomarker and safety data from all cohorts of the PRECISION-HD2 trial, including all patients from the 32 mg cohort, at the end of the first quarter in 2021.

PRECISION-HD1 trial: The PRECISION-HD1 trial is fully enrolled up to the 32 mg cohort. We expect to report biomarker and safety data from all completed cohorts up to and including the 16 mg cohort at the end of the first quarter in 2021.

Open-label Extensions of PRECISION-HD1 and PRECISION-HD2: In October 2019, we initiated an open-label extension ("OLE") of the PRECISION-HD2 trial outside of the United States for patients who participated in that trial. In February 2020, we also initiated an OLE of the PRECISION-HD1 trial outside of the United States for patients who participated in that trial. Along with data from the PRECISION-HD1 and PRECISION-HD2 trials, we expect to report data from patients who have received multiple doses of 8 or 16 mg of WVE-120101 or WVE-120102 in the OLE portions of the trials at the end of the first quarter of 2021.

WVE-003 clinical trial: In December 2020, we initiated clinical development of WVE-003 with the submission of a CTA. We expect to initiate dosing in a Phase 1b/2a clinical trial of WVE-003 of patients with HD in 2021.

Amyotrophic lateral sclerosis ("ALS") and frontotemporal dementia ("FTD"): In ALS and FTD, we are advancing WVE-004, which preferentially targets the transcripts containing the hexanucleotide G4C2 expansion in the *C9orf72* gene. WVE-004 is designed to minimize the impact on normal C9orf72 protein in patients, thereby reducing potential on-target risk. *In vitro*, WVE-004 potently and selectively reduced V3 transcripts in iPSC-derived motor neurons, which were derived from a patient carrying a C9orf72-repeat expansion. In C9 BAC transgenic mice, WVE-004 led to substantial reductions in repeat-containing C9orf72 transcripts and dipeptide repeat (DPR) proteins that are sustained for at least six months, without disrupting total protein expression.

WVE-004 clinical trial: In December 2020, we initiated clinical development of WVE-004 with the submission of a CTA. We expect to initiate dosing in a Phase 1b/2a clinical trial of WVE-004 for both patients with C9-ALS and patients with C9-FTD in 2021.

SCA3: In spinocerebellar ataxia 3 ("SCA3"), we are continuing to advance our program targeting *ATXN3*. SCA3 is a rare, hereditary (autosomal dominant), progressive, neurodegenerative disorder that is caused by a CAG-repeat expansion in the *ATXN3* gene.

Additional CNS Disorders: We are collaborating with Takeda to advance genetically defined targets for the treatment of other CNS disorders, including Alzheimer's disease and Parkinson's disease. Under the terms of the agreement, we may collaborate with Takeda

on up to six preclinical programs at any one time, during a four-year term. Takeda is entitled to exclusively license multiple preclinical programs from us during the term.

Duchenne Muscular Dystrophy ("DMD"): In DMD, we are advancing WVE-N531, which is designed to target exon 53 within the dystrophin gene. WVE-N531 is designed to cause the cellular splicing machinery to skip over this exon during pre-mRNA processing, which restores the dystrophin mRNA reading frame and enables production of truncated, but functional dystrophin protein. Exon-skipping produces dystrophin from the endogenous dystrophin gene (not micro or mini dystrophin expressed from a vector), under the control of native gene-regulatory elements, resulting in normal temporospatial expression. WVE-N531 will be our first splicing candidate incorporating PN backbone chemistry modifications to be assessed in the clinic.

WVE-N531 clinical trial: We expect to submit a CTA for WVE-N531 by the end of the first quarter in 2021.

Hepatic

Alpha-1 antitrypsin deficiency ("AATD"): We are leveraging our ADAR editing platform capabilities to develop a potentially novel treatment for AATD, which is a rare, inherited genetic disorder that is commonly caused by a G-to-A point mutation in the Z allele of the *SERPINA1* gene. This mutation leads to misfolding and aggregation of alpha-1 antitrypsin ("AAT") protein in hepatocytes and a lack of functional AAT in the lungs. People with AATD typically exhibit progressive lung damage, liver damage or both, leading to frequent hospitalizations and potentially terminal lung disease and/or liver disease. While the few approved therapies for AATD modestly increase circulating levels of AAT in those with the lung pathology, there are no approved therapies to address the liver pathology. Approximately 200,000 people in the United States and Europe are homozygous for the Z allele, which is the most common form of severe disease. In November 2020, we announced that our first ADAR editing program would be for AATD. Our novel RNA editing platform capability uses endogenous ADAR enzymes of A-to-I (G) base editing oligonucleotides, making this a potentially best-in-class modality for correcting the G-to-A disease-causing mutation in mRNA coded by the *SERPINA1* Z allele. By correcting the single RNA base mutation, ADAR editing may provide an ideal approach for increasing circulating levels of wild-type AAT protein and reducing aggregation in the liver, thus simultaneously addressing both the lung and liver manifestations of the disease.

In a primary hepatocyte *SERPINA1* Z cell model, we demonstrated that editing the Z allele mRNA back to wild-type prevents protein misfolding and increases secretion of edited AAT protein from hepatocytes. We expect to deliver *in vivo* data supporting the continued development of our AATD program in the first half of 2021.

Ophthalmology

In ophthalmology, we have generated *in vitro*, *ex vivo* and *in vivo* data in preclinical studies that support the potential of our stereopure oligonucleotides for the treatment of rare, inherited eye diseases. Our preclinical data demonstrate that a single intravitreal injection of stereopure oligonucleotide in the eye of non-human primates ("NHPs") resulted in greater than 95% knockdown of a target RNA in the retina for at least four months. Based on these data, our goal is to design candidates that could achieve a therapeutic effect with only two doses per year. Our pipeline includes two preclinical programs: Usher syndrome type 2A ("USH2A") and retinitis pigmentosa due to a P23H mutation in the *RHO* gene ("RhoP23H"). In September 2020, we presented *in vitro, ex vivo, and in vivo* preclinical data on our USH2A program, which is designed to promote USH2A exon 13 skipping, and we presented *in vitro* and *in vivo* data on our RhoP23H program, which is designed to selectively silence RhoP23H transcripts. We also presented results from our first achievement of ADAR editing in NHP retina *ex vivo* using stereopure oligonucleotides.

Note on the COVID-19 Global Pandemic

The ongoing COVID-19 global pandemic and variants thereof is having widespread, rapidly-evolving, and unpredictable impacts on global societies, economies, financial markets, and business practices. We are closely monitoring the impact of the pandemic and related developments, and our focus remains on safeguarding employee and patient health, while minimizing the negative effects on our business and continuing to advance the research and development of our therapeutic candidates. For discussion regarding the impact of the COVID-19 global pandemic on our business and financial results, see "Risk Factors" in Part I, Item 1A and "Management's Discussion and Analysis of Financial Condition and Results of Operations" in Part II, Item 7 of this Annual Report on Form 10-K.

Our Strategy

We are building a fully integrated genetic medicines company by leveraging PRISM to design, develop and commercialize optimized disease-modifying medicines for indications with a high degree of unmet medical need in genetically defined diseases. Our lead programs are focused in neurology and are aimed at addressing HD, ALS, FTD, and DMD. We are also pursuing additional CNS programs in collaboration with Takeda. Beyond neurology, our pipeline includes preclinical programs in hepatic diseases, including

AATD, and ophthalmology. In addition to driving clinical and preclinical programs, we are continuously investing in PRISM to fully unlock the potential of our unique and expanding platform capabilities.

The key components of our strategy are as follows:

- ***Maintain and extend our leadership in oligonucleotides***. We intend to establish a dominant position in the field of oligonucleotides, advancing basic research and pharmacology using stereochemistry across multiple therapeutic modalities and target classes. Through PRISM, our efforts continue to reveal structure-activity relationships among sequence, chemistry and backbone stereochemistry that may allow us to tune the activity of our oligonucleotides in a previously unexplored, modality-specific manner and use novel chemistry modifications, such as PN backbone chemistry.
- ***Rapidly advance our differentiated neurology portfolio.*** We are committed to transforming the care of rare, neurological genetic diseases. We are currently advancing five neurology development programs that are either in the clinic or anticipated to begin clinical trials in 2021. In HD, our three programs (WVE-120101, WVE-120102, and WVE-003) are designed to selectively target mHTT, while leaving wtHTT relatively intact. We are also advancing WVE-004 for the treatment of ALS and FTD and WVE-N531 for the treatment of Exon 53-amenable DMD. WVE-003, WVE-004, and WVE-N531 were all designed with novel PN backbone chemistry modifications developed from our PRISM platform. Finally, we are advancing multiple discovery-stage programs in collaboration with Takeda, including Alzheimer's disease and Parkinson's disease. We believe that the programs in our differentiated neurology portfolio have the potential to offer a foundation from which to transform our company into a leading genetic medicines company with a focus in neurology.
- ***Expand our pipeline using our genetic medicines "toolkit".*** We remain intent on making disciplined investments in our platform to enable a sustainable discovery and development engine for future growth. We believe PRISM will yield optimized oligonucleotide candidates to deepen our pipeline in neurology, hepatic, ophthalmology and other disease areas. Using PRISM, we are able to choose from multiple modalities (silencing, splicing, ADAR editing) to design novel approaches for the treatment of genetic diseases. We will continue to pursue these investments through wholly-owned programs as well as through potential partnerships and collaborations.
- ***Leverage manufacturing leadership in stereopure oligonucleotides.*** We have built a hybrid internal / external manufacturing model that gives us the capability to produce stereopure oligonucleotides at scales from one micromole to potential commercial scale. We believe that leveraging our internal manufacturing capabilities based in our Lexington, Massachusetts facility along with expertise from established contract manufacturing organizations ("CMOs") facilitates our growth and enhances our ability to secure drug substance for current and future development activities.

Oligonucleotides

The majority of traditional therapeutics, such as small molecules and biologics, work by interacting with proteins that contribute to the disease. However, there are thought to be a limited number of "druggable" proteins; it is currently estimated that approximately 80% of human protein targets cannot be addressed by these conventional approaches. In contrast, we believe that directing medicines to the RNA, which is critical to the production of proteins, rather than to the proteins themselves, has the potential to significantly increase the number of druggable targets. By intervening at the RNA level, we retain the ability to titrate dose, while avoiding permanent off-target genetic changes and other challenges associated with DNA editing or gene therapy approaches. We also believe that utilizing and building upon the established scientific, regulatory, operational and commercial knowledge base with regard to genetic medicines that target RNA gives us the best chance of success to rapidly deliver therapies to the patients who need them.

Nucleic acid therapeutics, including oligonucleotides, are an innovative class of drugs that can modulate the function of target RNAs to ultimately affect the production of disease-associated proteins or prevent the accumulation of pathogenic RNA species, which are emerging as important factors in human disease. Oligonucleotides can regulate protein and RNA via several different molecular mechanisms. These mechanisms can be broadly categorized as silencing, those that promote degradation of the target RNA, including antisense and RNAi; splicing, those that involve binding to the target RNA and modulating its function by promoting exon skipping; and ADAR-mediated RNA-editing.

The unique capability of oligonucleotides to address a wide range of genomic targets that impact multiple therapeutic areas creates potentially significant market opportunities for us to develop molecules to treat a broad spectrum of human diseases, including diseases where no medicines currently exist or for which existing treatments are not optimal.

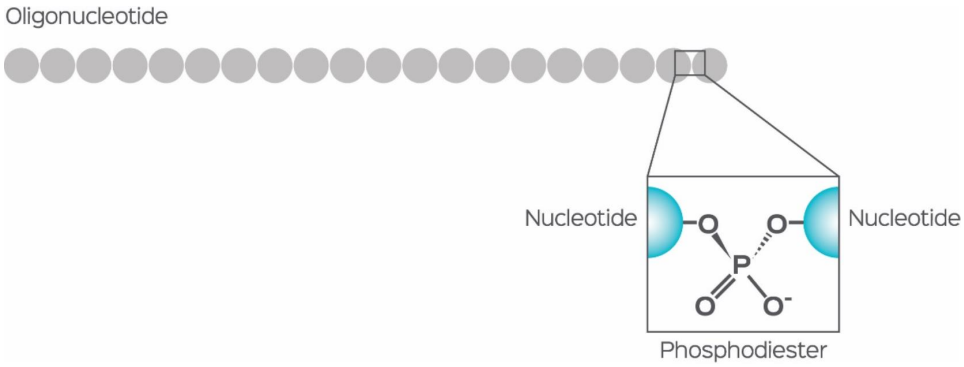
The oligonucleotides we are currently developing employ the following molecular mechanisms:

- **Antisense**, which uses a therapeutic oligonucleotide designed to bind to a specific sequence in a target RNA strand that encodes a disease-associated protein or pathogenic RNA. The resulting two-stranded molecule ("duplex") is then recognized by a cellular enzyme called RNase H, which cleaves, or cuts, the target RNA in the duplex, thereby preventing the disease-associated protein from being made.

- **RNA interference** (“RNAi”), which uses a therapeutic oligonucleotide designed to recognize a specific sequence and engages RNAi machinery known as the RNA-induced silencing complex (“RISC”) to silence a target RNA that is either pathogenic itself or encodes a disease-associated protein, thereby preventing the accumulation of the pathogenic species (RNA or protein).
- **Splicing / exon-skipping**, which is the processing of a nascent pre-mRNA transcript into messenger RNA (“mRNA”) by removing introns and joining exons together. Exon skipping uses a therapeutic oligonucleotide designed to bind to a particular sequence within a target pre-mRNA and direct the cellular machinery to delete, or splice out, certain specific regions of that RNA. Often, the underlying mutation leads to non-productive mRNA, yielding no functional protein. Use of the exon-skipping modality permits the cellular machinery to bypass and assemble a partially functional protein, thereby mitigating or alleviating the disease that would otherwise result.
- **ADAR-mediated RNA editing,** which involves a therapeutic oligonucleotide that uses endogenous ADAR (adenosine deaminases acting on RNA) to edit Adenosines in target RNAs. This technology can be used to correct missense and nonsense mutations to restore or modify protein activity. Other applications of this technology include the ability to target AUGs in the 5’-UTR for translational upregulation, target AG splice acceptor sites to modify exon splicing, and target amino acids (codons) to alter their function, examples of which include amino acids involved in post-translational modifications, to synthetically alter signaling pathways and/or protein stability, or post-translational protein processing, such as altering a protease cleavage sequence.

Oligonucleotide Backbone Modifications Result in Complex Drug Mixtures

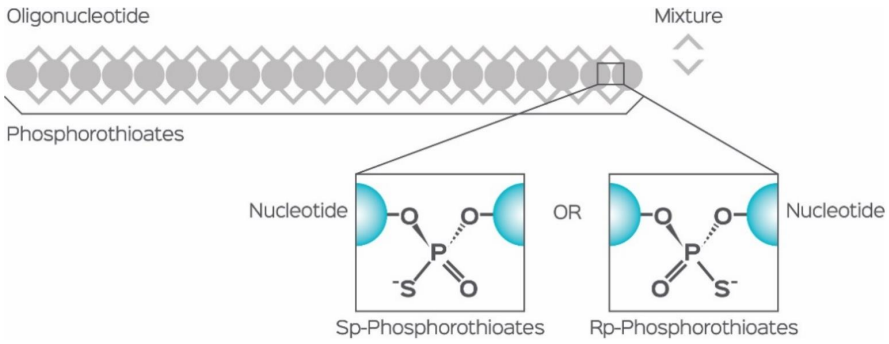
Oligonucleotides are comprised of a sequence of nucleotides—the building blocks of RNA and DNA—that are linked together by a backbone of chemical bonds. In nucleic acid molecules that have not been modified for therapeutic use, the nucleotides are linked by phosphodiester (“PO”) bonds, as shown below.



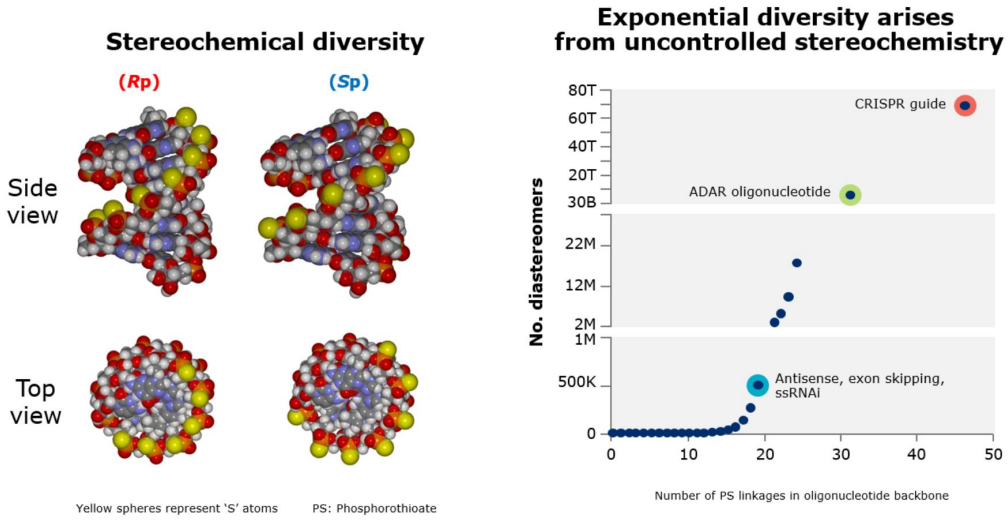
Such unmodified nucleic acid molecules are unsuitable for use as therapeutics because they are rapidly degraded, are rapidly cleared by the kidneys and are taken up poorly by targeted cells.

Backbone chemistry modifications such as the phosphorothioate (“PS”) modification, one of the most common backbone modifications used in oligonucleotides, can improve the stability, biodistribution and cellular uptake of oligonucleotides.

A consequence of introducing backbone modifications, such as PS modifications, into an oligonucleotide is that it also introduces a chiral center at each phosphorus, creating stereoisomers designated as either an “*S*p” or “*R*p” isomer. As shown below, these stereoisomers have identical chemical compositions but different three-dimensional arrangements of their atoms and consequently have different chemical and biological properties.



During traditional oligonucleotide synthesis, the isomeric configuration at each chiral backbone modification is random (either *R*p or *S*p). Because oligonucleotides contain a string of nucleotides with associated chiral backbone modifications, the synthesis process generates a complex mixture containing many stereoisomers. Using PS modifications as an example, each PS linkage doubles the number of stereoisomers in the product, so that a traditional preparation of a PS-containing oligonucleotide contains 2^N stereoisomers, where N represents the number of PS modifications. As shown below, a traditional, fully PS-modified antisense oligonucleotide (20 nucleotides in length, 19 PS modifications) is a mixture of over 500,000 stereoisomers, each having the same nucleotide sequence but differing in the stereochemistry along their backbones.



Stereoisomers can possess different chemical and pharmacological properties. For example, certain stereoisomers can drive the therapeutic effects of a drug while others can be less beneficial or can even contribute to undesirable side effects. The greater the variation among a drug's constituent stereoisomers, the greater the potential to diminish the drug's efficacy and safety when it's a complex mixture.

Prior to the development of our technology, it was not possible to create stereopure oligonucleotides, meaning molecules where the configuration of each chiral backbone linkage is precisely controlled during chemical synthesis. Moreover, because of the sheer number of stereoisomers present in a mixture, it would be impractical, if not impossible, to physically isolate the most therapeutically optimal stereoisomer from within a mixture. For these reasons, all chiral backbone-modified oligonucleotides currently on the market and in development by others are mixtures of many stereoisomers, which we believe are not optimized for stability, catalytic activity, efficacy or toxicity.

In small molecule therapeutics, U.S. regulators have long sought to eliminate the risks potentially posed by drug mixtures containing multiple stereoisomers. Since 1992, the FDA has recommended full molecular characterization of stereoisomers within small-molecule drug mixtures. Historically, it has not been possible to achieve such characterization for nucleic acid therapeutic drug mixtures, which can contain tens of thousands to millions of distinct pharmacological entities. Based on our published and ongoing preclinical studies, we believe that we can design and synthesize stereopure chemically modified oligonucleotides that demonstrate superior pharmacological properties compared with mixture-based oligonucleotides. We believe that PRISM has the potential to set a new industry standard for the molecular characterization of complex nucleic acid therapeutic drug mixtures.

We continue to develop new types of backbone modifications, other than PS modifications, that can be chirally controlled with our technology.

PRISM: Our proprietary discovery and drug development platform

Through PRISM, our proprietary discovery and drug development platform, we have discovered and expect to continuously elaborate on the relationships between the chemical makeup of an oligonucleotide, including the three-dimensional orientation or arrangement of its atoms, and its pharmacology (i.e., stability of the drug, activity against the target, specificity for the target and safety of the drug). In addition, we have defined relationships between various 2'-sugar modifications to the nucleotide (such as methoxy, methoxyethyl, fluoro, locked), and the stereochemistry of the backbone that enhances oligonucleotide pharmacology, providing an enhanced therapeutic profile.

Our rational process for designing stereopure oligonucleotides, which is based on the interplay among oligonucleotide sequence, chemistry and backbone stereochemistry, allows us to selectively optimize for the molecular mechanism in order to generate best-in-class oligonucleotides. With PRISM, we leverage the diversity created by backbone stereochemistry to expand the parameters that we explore to optimize oligonucleotides. We are using these ongoing discoveries to guide our drug development activities, which we believe will lead to medicines that are more specific, can be dosed at lower concentrations, less frequently, or some combination of these characteristics as well as with improved therapeutic profiles.

Advantages of Our Approach

We believe that PRISM is a significant advancement in the development of oligonucleotides. The advantages of our approach include:

- ***Ability to rationally design product candidates with optimized pharmacological properties***. PRISM, our proprietary discovery and drug development platform, enables us to target genetically defined diseases with stereopure oligonucleotides across multiple therapeutic modalities. PRISM combines our unique ability to construct stereopure oligonucleotides with a deep understanding of how the interplay among oligonucleotide sequence, chemistry and backbone stereochemistry impacts key pharmacological properties. By exploring these interactions through iterative analysis of *in vitro* and *in vivo* outcomes and machine learning-driven predictive modeling, we continue to define design principles that we deploy across programs to rapidly develop and manufacture clinical candidates that meet pre-defined product profiles. PRISM has also enabled us to further innovate our nucleic acid chemistry, including the application of novel PN chemistry back bone modifications to our pipeline programs.
- ***Broad applicability***. PRISM is applicable to oligonucleotides acting via multiple molecular mechanisms, including antisense, RNAi, exon skipping, splicing, ADAR-mediated RNA editing, microRNA and others, and is compatible with a broad range of chemical modifications and targeting moieties.
- ***Proprietary production of stereopure oligonucleotides***. Our scientists have developed expertise in the techniques required to produce adequate supplies of chemically modified stereopure oligonucleotide materials for our preclinical and planned clinical activities. In addition, we believe we have the intellectual property position and know-how necessary to protect, advance and scale these production processes to support our clinical trials and potential future commercial supply.
- ***Scalability and Manufacturing.*** Our manufacturing process and technical expertise in designing stereopure oligonucleotides is unique. We believe that our scalable synthesis processes will allow us to meet demand for cGMP-qualified clinical trial supply, as well as the potential for commercial manufacturing at a cost of goods and potential cost-per-patient that are comparable to stereorandom oligonucleotides.

Our Proprietary Chemistry

Backbone Stereochemistry

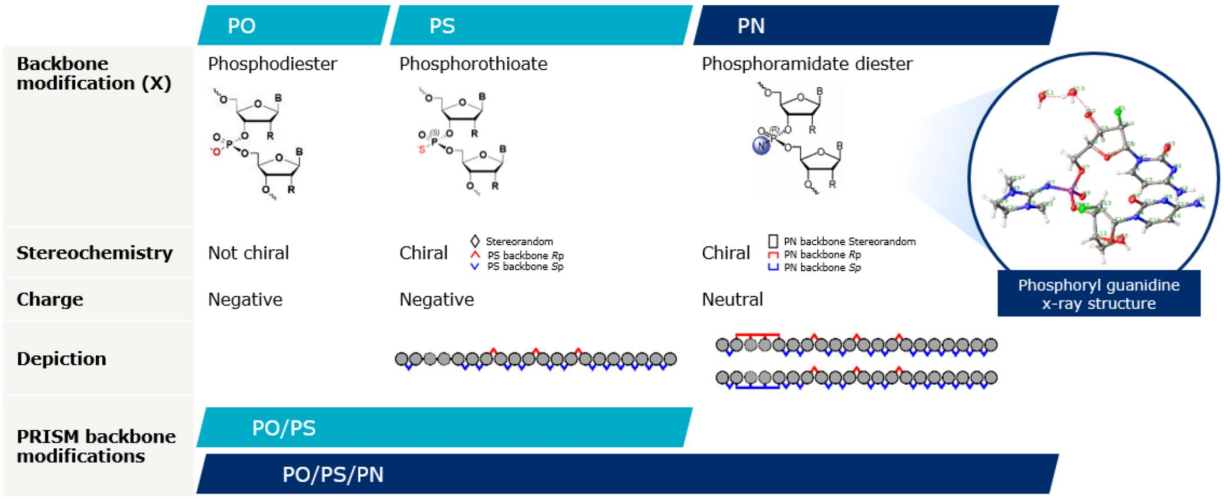
In our *Nature Biotechnology* paper (Iwamoto N, et al. Nature Biotechnol. 2017;35(9):845-851), we described our studies using our proprietary chemistry to design and synthesize stereopure oligonucleotides and oligonucleotide mixtures based on mipomersen. These and other preclinical studies have demonstrated that stereochemistry and pharmacology are directly related, and that by controlling stereochemistry, we can impact multiple aspects of pharmacology, including stability, catalytic activity, efficacy, specificity, and safety. We studied mipomersen because, at that time, it was the only systemically administered nucleic acid therapeutic approved for commercialization, and documents from the regulatory bodies that evaluated mipomersen for marketing approval were publicly available. Mipomersen (formerly marketed under the brand name Kynamro, now discontinued) received FDA approved for the treatment of homozygous familial hypercholesterolemia in 2013 and is designed to silence production of Apolipoprotein B (“APOB”) via an antisense mechanism.

Mipomersen, an oligonucleotide containing 20 nucleotides and 19 PS modifications, is synthesized by traditional oligonucleotide chemistry; thus, it is a mixture of over 500,000 different stereoisomers (2^{19} = 524,288). We rationally designed and synthesized individual stereoisomers of mipomersen, each having position-specific and distinct stereochemistry, and conducted studies comparing these defined stereoisomers with the mipomersen stereomixture.

We have subsequently published additional evidence supporting the idea that stereopure oligonucleotides can be developed to have superior pharmacology to stereorandom including in our *Translational Vision Science & Technology* paper (Byrne M, et al. Trans Vis Sci Tech. 2021; 10(1):23) and our *Nature Communications* paper (Liu Y, et al. Nature Communications. 2021; 12:847), which are discussed in more depth in the “Business - Therapeutic Programs - Ophthalmology” and “Business - Therapeutic Programs - Amyotrophic Lateral Sclerosis and Frontotemporal Dementia” sections, respectively.

PN Backbone Chemistry Modifications

Our initial investigations into backbone chemistry and stereochemistry on oligonucleotide pharmacology focused on the widely used PO and PS backbones because they are amenable to all nucleic acid modalities. In August 2020, we announced the introduction of novel PN backbone chemistry modifications ("PN") to our repertoire of backbone modifications, which involve replacing a non-bridging oxygen atom with a nitrogen-containing moiety, as shown below.

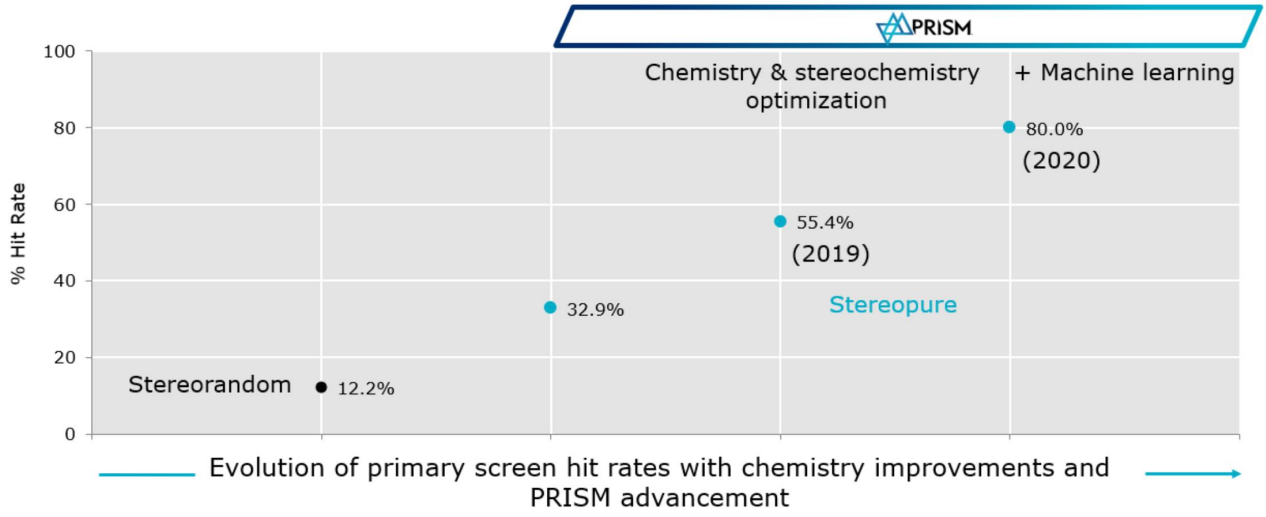


Molecule structure illustrative of backbone modification patterns

Specifically, we have incorporated one of these PN modifications – which contains phosphoryl guanidine – into oligonucleotide compounds. As with PS modifications, PN modifications are chiral and we have the capacity to control PN backbone stereochemistry. Unlike PS modifications, PN modifications are neutral, meaning that the negative charge of the oligonucleotide is reduced with every PN modification added to the backbone. In preclinical experiments, we have demonstrated that judicious use of PN backbone chemistry modifications in stereopure oligonucleotides have generally increased potency, tissue exposure and durability across our silencing, splicing and editing modalities.

Applications of PRISM Across Multiple Therapeutic Modalities

Using PRISM, we have designed and optimized diverse sets of stereopure oligonucleotides, which allows us to characterize and compare the behavior of various stereoisomers. With each new target, we gain insight into how the interplay between sequence, chemistry, including 2'-modifications and backbone chemistry, and stereochemistry impacts activity, and we build these learnings into our future programs. Hit rates, defined as the percentage of total oligonucleotides screened that yielded activity in the screening assay, in our primary screens performed with oligonucleotides in a stereorandom format have ranged from 10% to 15%. By applying learnings from early programs to generate new screening formats, hit rates have risen, with our most productive screens reaching hit rates of up to 80%. This improving hit rate illustrates that the right combination of chemistry and stereochemistry can yield activity through sequences that would be inactive or only mildly active in a stereorandom format, supporting our belief that the activity of oligonucleotides depends on an interplay between sequence, chemistry and backbone stereochemistry.



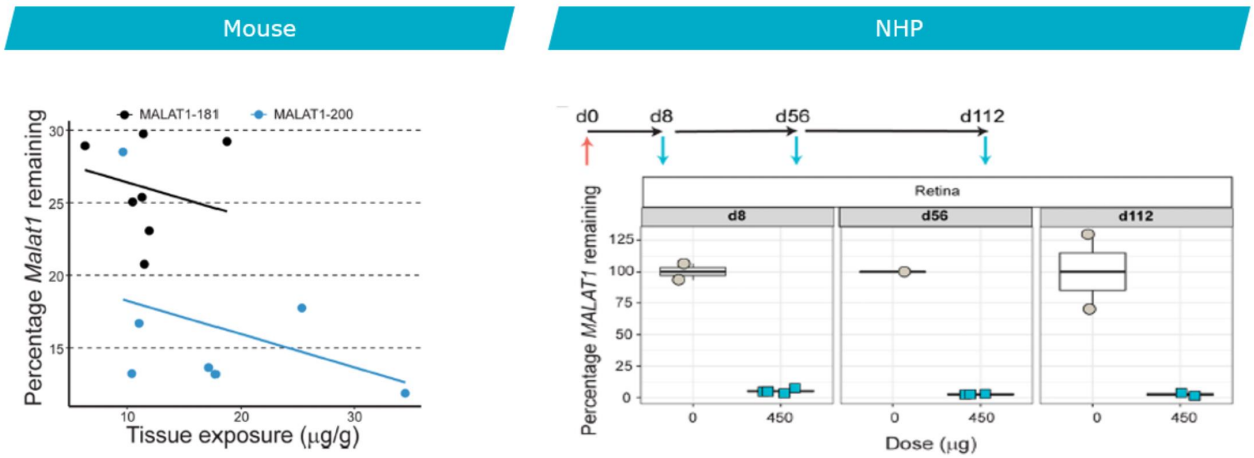
In the next section, we describe three distinct modalities for which we have used PRISM to optimize stereopure oligonucleotides.

Silencing - RNase H-mediated degradation

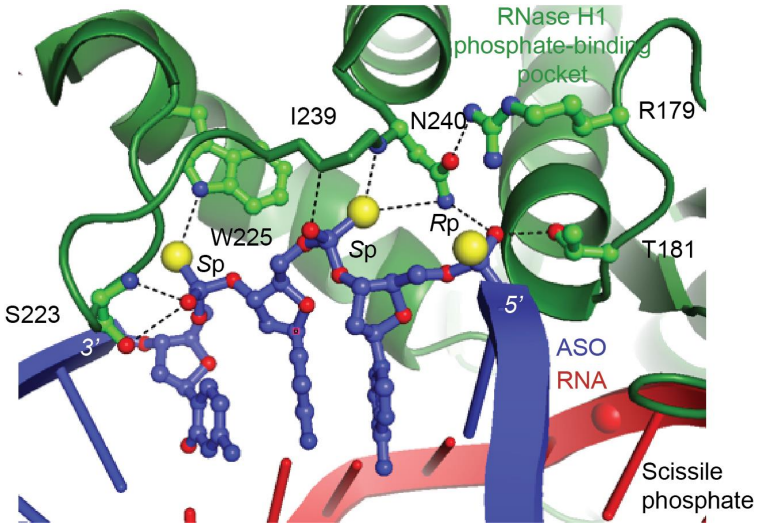
We have used *Malat1*, a long noncoding RNA that is ubiquitously expressed and enriched in the nucleus, as a proof-of-concept target for our RNase H-silencing programs. Using PRISM, we can produce stereopure oligonucleotides that promote potent and specific RNase H activity in preclinical experiments.

In our *Translational vision science & technology* paper (Byrne M, et al. Trans Vis Sci Tech. 2021;10(1):23), we describe an optimized stereopure antisense oligonucleotide, MALAT1-200, that shows enhanced potency, efficacy, and durability of MALAT1 RNA depletion in the eye compared with its stereorandom counterpart, MALAT1-181, in mouse and NHP eyes upon IVT injection. Because MALAT1-200 shares the same sequence and chemical modification pattern as MALAT1-181, it represents one stereoisomer of the more than 65,000 stereoisomers that comprise MALAT1-181. These results provide proof of concept, consistent with our prior work, that the identification of stereoisomers with desirable activity profiles can yield benefits over mixtures of randomly generated stereoisomers.

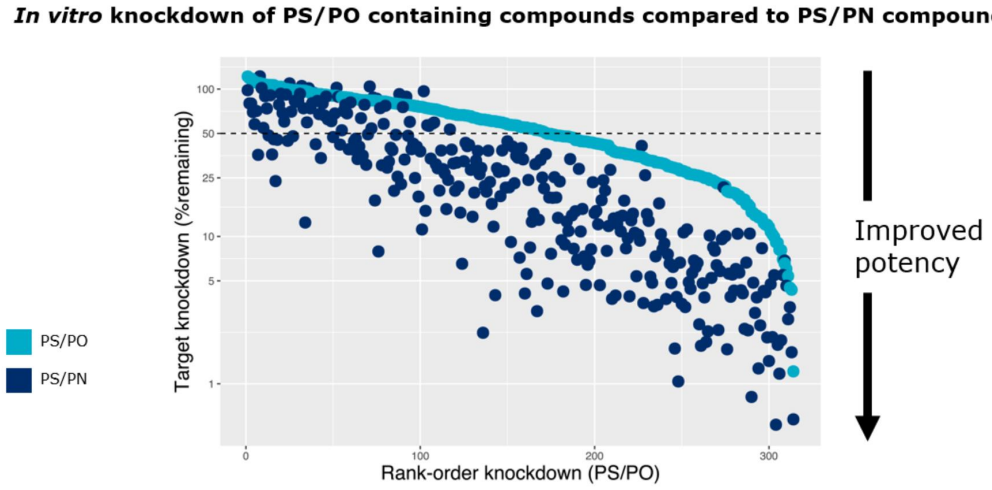
In the figure below on the left, the PK-PD relationship is shown for stereorandom (50 ug) and stereopure (50 ug) oligonucleotides in the posterior position of the eye at 1 week. The percentage of Malat1 remaining is plotted with respect to the concentration of oligonucleotide detected in the tissue (n=7); each point represents data from one treated eye. The stereopure oligonucleotide was more active than the stereorandom oligonucleotide, and we also observed greater tissue exposure with the stereopure oligonucleotide than the stereorandom. In the figure below on the right, the schematic representation of a longer-term study in NHPs is shown, which evaluated the durability of a single 450 ug dose of stereopure oligonucleotide. Animals were dosed with a single 450 ug IVT injection on day 0 (d0) and samples were evaluated on days 8 (d8, 1 week later, blue arrows), 56 (d56, 2 months later), and 112 (d112, 4 months later). MALAT1 expression at d8, d56, and d112 after treatment with phosphate-buffered saline ("PBS") (beige, 0 ug) or stereopure oligonucleotide (blue, MALAT1-200) in NHP retina. At 1 week, 2 months, and 4 months post injection, MALAT1 RNA levels in the treated retina were decreased by ~95% compared with PBS-treated control.



We have determined the X-ray crystal structure to a resolution of 1.3 Å (shown below) of RNase H1 (green) bound to a heteroduplex containing a surrogate target mRNA (red) and a stereopure oligonucleotide (blue). In our *Nature Biotechnology* paper, we predicted that amino acids in the RNase H1 phosphate-binding pocket would make stereochemically differentiated contacts with three consecutive phosphates in the oligonucleotide backbone. In this structure, the phosphate-binding pocket is shown to contact the 3'-*Sp*-*Sp*-*Rp*-5' phosphorothioate linkages in the stereopure oligonucleotide. This structure confirms our hypothesis and supports our findings that optimal placement of backbone stereochemistry in an oligonucleotide can provide control over the activity of RNase H1.

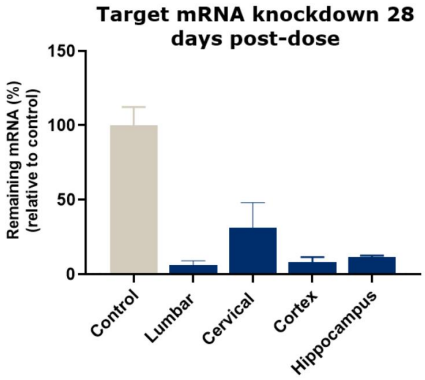


To illustrate the impact of PN backbone chemistry modifications for a silencing modality, we performed screens for identifying RNaseH-targeting sequences in iCell neurons in vitro using free uptake. This screen was initially performed with stereopure molecules with PS and PO backbone chemistry modifications, and the oligonucleotides are rank-ordered from left to right according to their potency. Next, we performed a head-to-head comparison with molecules that contained the same sequence and the same 2'-ribose chemistry, but with the addition of PN chemistry at select locations in the backbone. The introduction of a few PN linkages signficantly increases the potency of the vast majority of the stereopure PS / PO molecules, with ~80% of them yielding at least 75% knockdown. These results, shown below, suggest we are able to target sequence space that would otherwise be inaccessible.



Moving *in vivo*, the incorporation of PN backbone chemistry modifications has had a significant impact on our silencing molecules. In the results shown below for an undisclosed target, non-human primates received a single 12 mg dose by intrathecal injection. One month after administration, we observed that the candidate was widely distributed across the CNS, including the spinal cord, cerebral cortex and hippocampus. This single dose led to approximately 90% knockdown of the target mRNA across CNS tissues.

Substantial and widespread target mRNA reduction following single intrathecal dose in NHPs

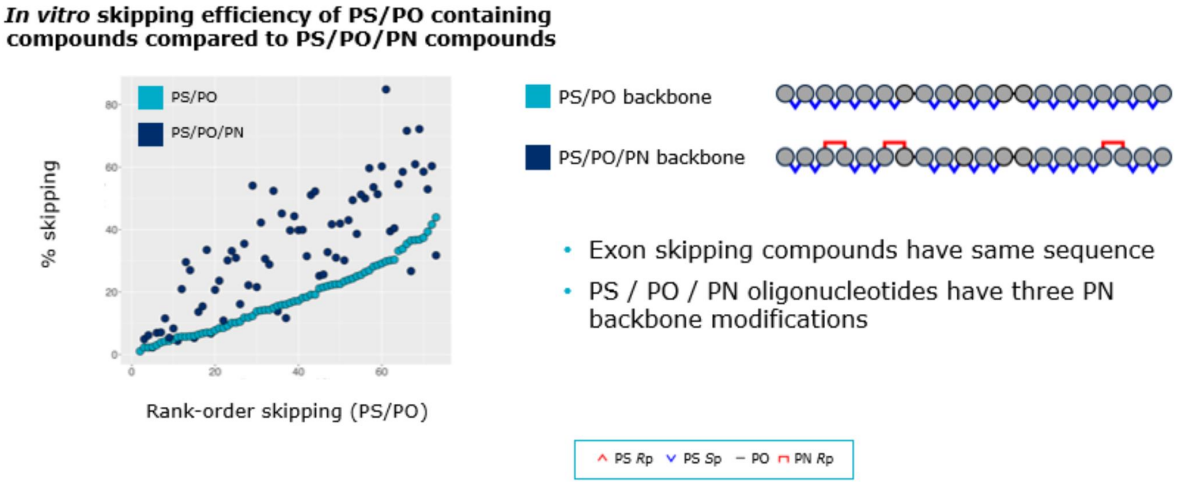


- Single IT dose of 12 mg (n=3)
- Therapeutic candidate widely distributed across brain and spinal cord
- ~90% mRNA knockdown one-month following single dose

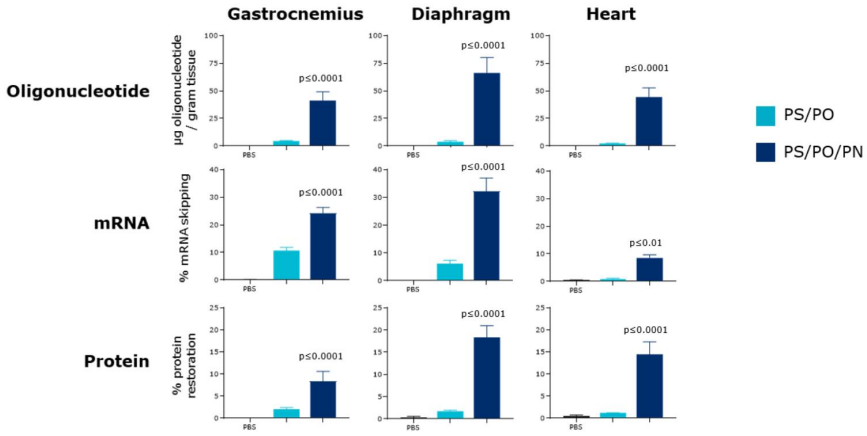
Splicing - exon skipping

With PRISM, we have optimized stereopure oligonucleotides that promote efficient exon skipping *in vitro* and *ex vivo*. In our exon-skipping programs, as with our other modalities, the sequence, chemistry and backbone stereochemistry of oligonucleotides impact their activity.

To highlight the impact of PN chemistry on exon skipping, we plotted the in vitro skipping efficiency of compounds containing PS / PO backbone chemistry modifications, depicted in the graph below by the teal dots, which are rank-ordered from left-to-right based on their exon-skipping potency in myoblasts. The more potent molecules are shifted upwards as they are restoring expression. The navy dots represent the impact of a few stereopure PN modifications in compounds with otherwise identical sequences and 2'-ribose chemical modifications. There is an overall shift upwards in activity among the PS / PO / PN compounds, representing a substantial potency gain in most cases.



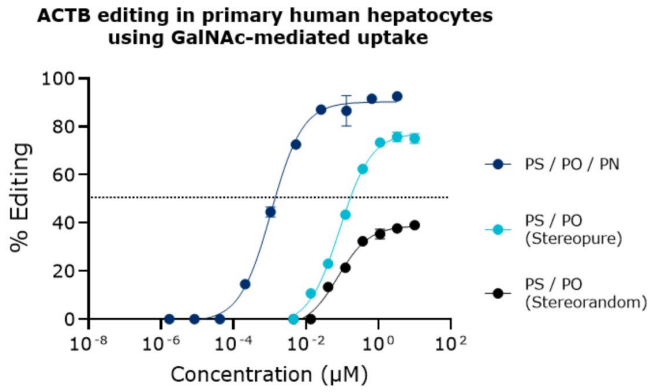
In a six-week study in a double-knockout "dKO" mouse model, weekly doses of 75 mg / kg PN-containing compounds (shown below in navy) or PS / PO modifications (shown below in light blue), were administered to assess the PK-PD relationship for both types of compounds. We found that the PN-containing compounds accumulated to higher levels in all muscle types compared with the PS / PO compounds (as shown below, top graphs). The PN-containing compounds also led to more exon skipping (as shown below, middle graphs) and more dystrophin restoration (as shown below, bottom graphs) in all muscles, but especially in the heart and diaphragm. These results demonstrate the impact of a few PN linkages – with no delivery vehicle or conjugate – significantly improves the PK-PD profiles for stereopure compounds.



Editing - ADAR-mediated RNA editing

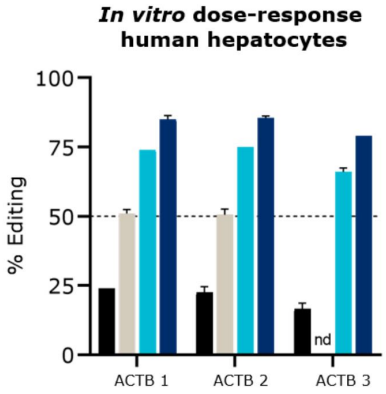
Most recently, we have applied our PRISM platform to the generation of RNA-editing oligonucleotides. In preclinical studies, we have evaluated thousands of oligonucleotides, assessing a variety of sugar or base modifications, backbone chemistry and stereochemistry, and other parameters such as oligonucleotide length to produce insight into the relationship between an oligonucleotide's structure and its ability to elicit ADAR-editing activity.

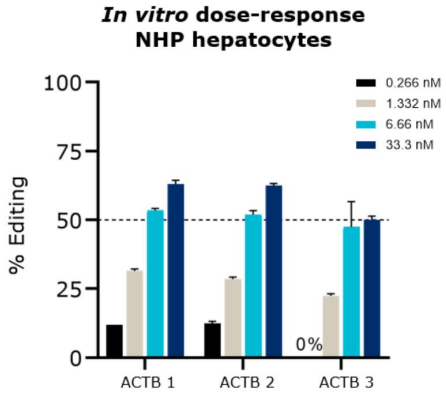
With PRISM, we have generated stereopure antisense oligonucleotides, optimized for chemistry and stereochemistry, that promote RNA editing with endogenous adenosine deaminase acting on RNA (ADAR) enzymes in cellular models. As shown in the figure below, we show the activity of beta-actin-editing stereopure oligonucleotides, with and without PN linkages, compared to a matched stereorandom oligonucleotide (shown in black) in primary human hepatocytes. These oligonucleotides are GalNAc conjugated to increase uptake in hepatocytes. The addition of PN chemistry substantially improves both potency and editing efficiency.



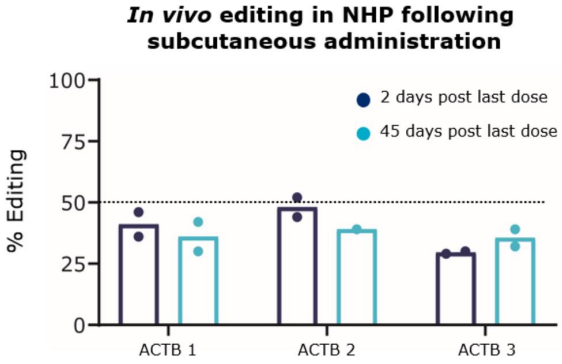
Data from independent experiments

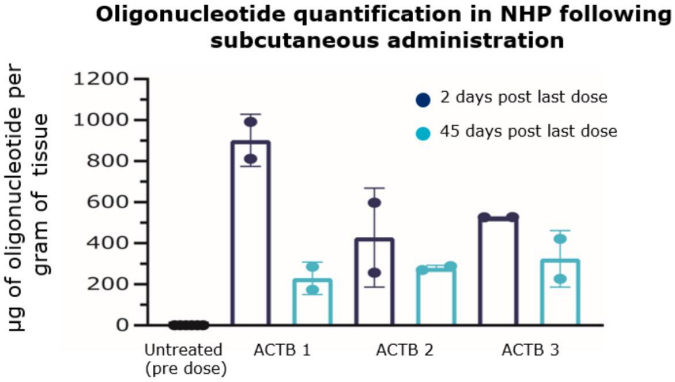
We have achieved efficient RNA editing in vitro with our oligonucleotides across a variety of cell lines, including non-human primate and human primary hepatocytes, as shown in the figures below. We observed potent, dose-dependent RNA editing with three chemically distinct stereopure oligonucleotides via GalNAc-mediated uptake.





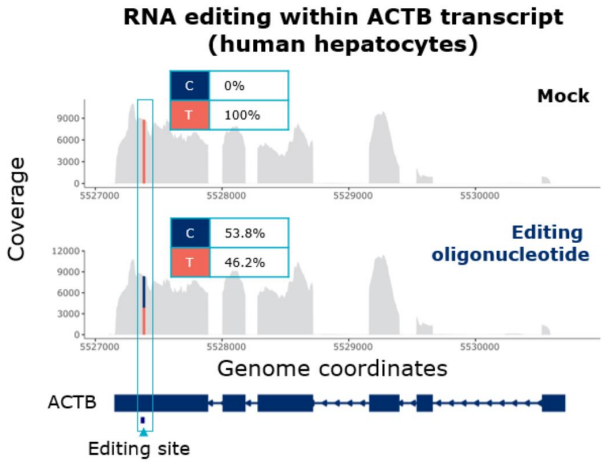
We next evaluated these same *ACTB*-editing oligonucleotides in vivo in NHPs, and the results are shown in the figures below. For this study, we dosed NHPs subcutaneously once a day for five days. We took liver biopsy samples at baseline at two days and 45 days after the last dose to evaluate editing. We detected up to 50% editing two days after the last dose as compared to a baseline of 0% editing, as shown in the figure below on the left. These editing results were durable: we continued to see significant editing 45 days after the last dose. The pharmacokinetic data, shown in the figure below on the right, confirmed that a significant amount of oligonucleotide was still detectable in the liver at that time.

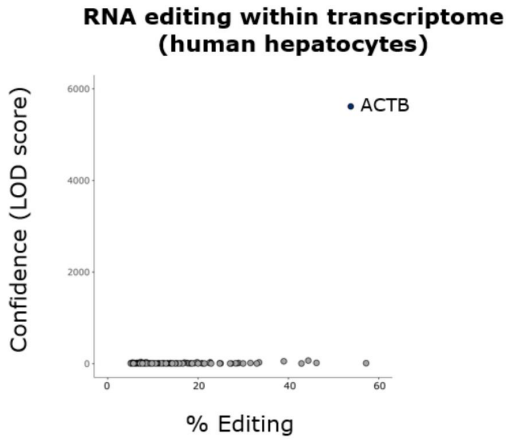




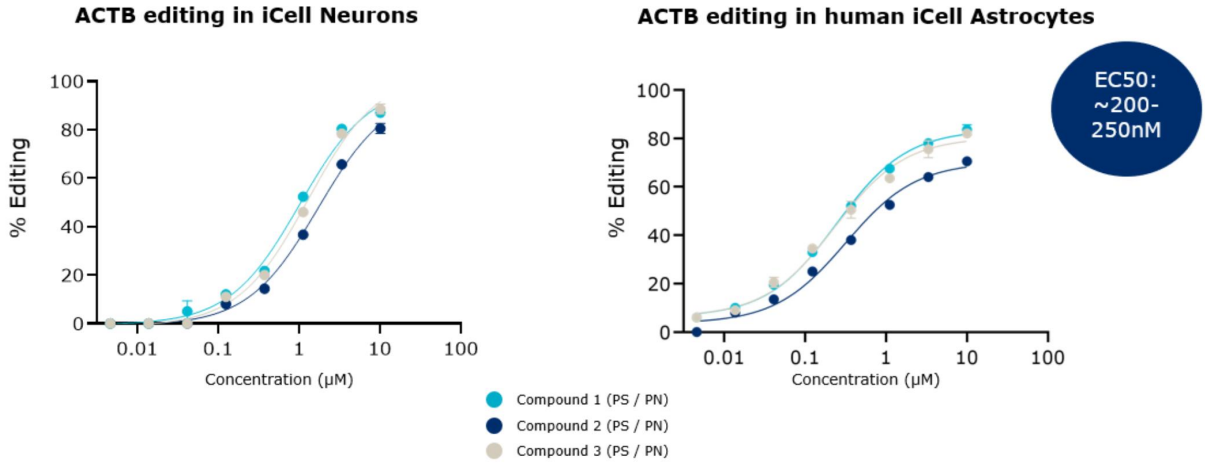
To evaluate the specificity of ADAR-editing oligonucleotides, we performed RNA-seq in primary human hepatocytes. In the figure below on the left, the total sequence coverage across the entire ACTB transcript for the mock-treated group (top) and oligonucleotide-treated samples (bottom) are shown. Editing was only detected at the targeted sequence in the actin transcript and the percentage of unedited “T” and edited “C” reads are indicated for each group.

To assess off-target editing for the whole transcriptome, a mutation-calling software was used to call edit sites. From this analysis, we observed nominal off-target editing across the transcriptome. Sites where potential off-target editing occurred mapped predominately to non-coding regions of the transcriptome, and had either low read coverage in the analysis or occurred at low percentages of less than 10%, indicating that these are relatively rare events, as shown in the figure below on the right.

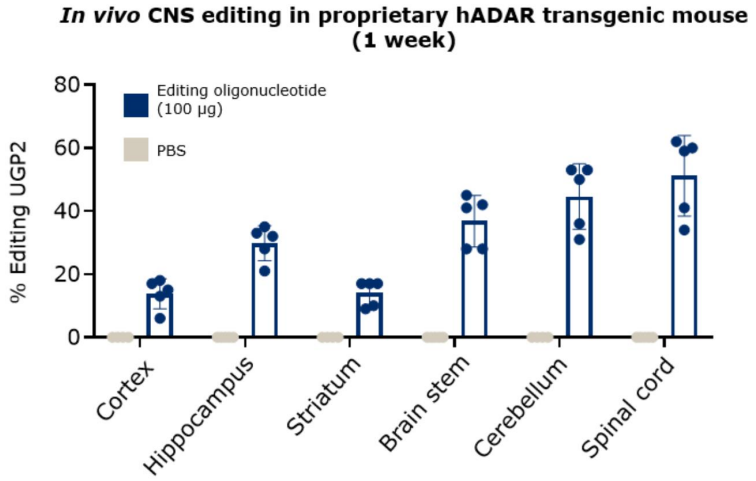




We intend to apply our RNA-editing modality to neurology, and we have assessed editing activity in vitro in both neurons and astrocytes. Our PN-containing stereopure molecules elicited efficient editing in both iCell neurons and iCell astrocytes, with EC50s for astrocytes reaching the 200 nM range in vitro, as shown in the figures below. These potencies were obtained with chemical modifications to the oligonucleotides alone under free uptake conditions. There was no delivery vector and no conjugate used in these experiments.



We have also evaluated editing activity with PN-containing stereopure oligonucleotides after a single injection into the CNS of a proprietary humanized mouse model, as shown in the figure below. We observed editing activity across CNS with 50% or more editing activity in many tissues. These results are preliminary findings evaluating editing of UGP2, a transcript that is more challenging to edit efficiently than ACTB.



Therapeutic Programs

Our most advanced therapeutic programs are in neurology. We have ongoing clinical trials of our two initial programs in HD (WVE-120101 and WVE-120102) and will initiate clinical trials for a third program in HD (WVE-003), our C9orf72 program in ALS and FTD (WVE-004), and our exon 53 program in DMD (WVE-N531) in 2021. We continue to advance our ATXN3 program in SCA3. We are also pursuing additional CNS programs, including Alzheimer's disease, Parkinson's disease, and others, in collaboration with Takeda. Beyond neurology, we are advancing our first ADAR editing program in alpha-1 antitrypsin disorders. We are also evaluating ophthalmology programs and continue to explore additional targets in neurology and hepatic disorders.

See below for more information on these programs and the diseases we are targeting.

Huntington's Disease

Background and Market Opportunity

Huntington's Disease ("HD"): HD is a rare hereditary neurodegenerative disease that results in early death and for which there is no cure. HD is caused by a mutation (i.e., an expanded CAG triplet repeat) in the HTT gene, which results in production of mutant HTT ("mHTT") protein. In HD patients, there is a progressive loss of neurons in the brain leading to cognitive, psychiatric and motor disabilities. HD patients still possess wild-type (healthy) HTT ("wtHTT") protein, which is important for neuronal function, and there is increasing evidence that wtHTT may be neuroprotective in an adult brain. Additionally, a dominant gain of function in mHTT protein and a concurrent loss of function of wtHTT protein may be important components of the pathophysiology of HD. Accordingly, suppression of wtHTT may have detrimental long-term consequences. A 2020 *Nature* publication (Poplawski, G.H.D., et al. Injured adult neurons regress to an embryonic transcriptional growth state. *Nature* 581, 77–82 (2020)) described results that involved conditional knockout of huntingtin in 4-month old mice (post-neuronal development), which demonstrated that huntingtin is at the center of the regeneration transcriptome and played an essential role in neural plasticity. In October 2019, at our Analyst and Investor Research Day, key opinion leaders in HD research presented data suggesting that wtHTT is neuroprotective in an adult brain; transport of key neurotrophic factors such as brain-derived neurotrophic factor ("BDNF") are regulated by wtHTT levels; and HD may be caused by a dominant gain of function in mHTT and a loss of function of wtHTT protein. Further, the relative proportion of wtHTT to mHTT is critical based on evidence that suggests increased amount of wtHTT relative to mHTT may result in slower disease progression (measured by age-at-onset). Also, HD patients that lack wtHTT all together have significantly more severe disease, as measured by disease progression after symptom onset.

Symptoms of HD typically appear between the ages of 30 and 50 and worsen over the next 10 to 20 years. Many describe the symptoms of HD as similar to having amyotrophic lateral sclerosis, Parkinson's Disease and Alzheimer's Disease simultaneously. Patients experience a reduction in motor function and psychological disturbances. Life expectancy after symptom onset is approximately 20 years. In the most symptomatic stages, often lasting over 10 years, affected persons become fully dependent upon others to manage all activities of daily living; they lose the ability to make decisions, feed themselves and walk, often requiring premature placement in a long-term care facility. It is estimated that approximately 30,000 people in the United States have symptomatic HD. Our allele-selective approach may also enable us to address the pre-manifest, or asymptomatic, HD patient population in the future. More than 200,000 people in the United States are at-risk of developing HD.

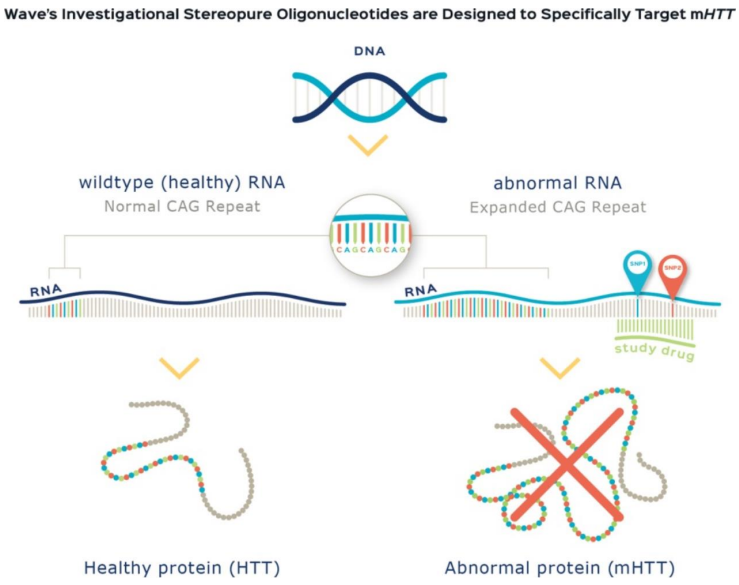
Current Treatments

There are no approved treatments that can reverse or slow HD progression. Current pharmacological therapies only address HD symptoms. Antipsychotics are used to manage depression, irritability and chorea (involuntary movements). Xenazine (tetrabenazine) and Austedo (deutetrabenazine) are the only two therapies approved for the treatment of chorea associated with HD in the United States.

Our Programs

Our HD Portfolio: In HD, we are currently advancing three clinical programs. WVE-120101 and WVE-120102 are our first clinical programs in HD, where each is a distinct stereopure antisense oligonucleotide designed to selectively target a single nucleotide polymorphism ("SNP") associated with the disease-causing mutant huntingtin (mHTT) mRNA transcript within the *HTT* gene: rs362307 ("mHTT SNP1") and rs362331 ("mHTT SNP2"), respectively. Our third program in HD, WVE-003, is also a stereopure antisense oligonucleotide designed to target an undisclosed SNP3, "mHTT SNP3." WVE-003 incorporates our novel PN backbone chemistry modifications, as well as learnings from the first two HD programs. We initiated clinical development of WVE-003 with the submission of a clinical trial application ("CTA") in December 2020. Approximately 50% of the HD population carries SNP1 or SNP2, and, with overlap, up to 70% of the HD population carries SNP1, SNP2 or both. Approximately 40% of the HD population carries SNP3, and, with overlap, up to 80% of the HD population carries at least one of SNP1, SNP2 and/or SNP3. Targeting mRNAs with these SNPs allows us to lower expression of transcript from the mutant allele, while leaving the healthy transcript relatively intact. The healthy transcript is required to produce wtHTT protein which is important for neuronal function. We commonly refer to this method (or approach) as "allele-selective targeting." SNPs are naturally occurring variations within a given genetic sequence and in certain instances can be used to distinguish between two related copies of a gene where only one is associated with the expression of a disease-causing protein. Our allele-selective approach may also enable us to address the pre-manifest, or asymptomatic, HD patient population in the future. We have shown that by targeting mHTT SNP1 and mHTT SNP2 in preclinical *in vitro* studies, the production of disease-causing proteins associated with HD can be selectively reduced. In addition, we have shown that by targeting mHTT SNP3 in preclinical *in vitro* studies, WVE-003 selectively reduces the expression of mHTT, and by targeting mHTT SNP3 in preclinical *in vivo* studies, WVE-003 demonstrated durable and potent knockdown of mHTT mRNA.

For all three of our HD programs, we have demonstrated *in vitro* that these oligonucleotides preferentially target the mHTT transcript, while leaving the wtHTT mRNA largely intact in human neuronal systems. The ability of these oligonucleotides to reduce mHTT mRNA is dependent on the specific positioning of the *R*p stereochemistry.



SNP Phasing Technology: To verify that HD patients have at least one of the SNPs that we are targeting on the mutant allele, we investigated multiple technologies that could provide highly accurate results and rapid turnaround. We conducted a prospective observational study of the frequency of SNP1 and SNP2 in patients with HD, which confirmed the feasibility of rapidly and prospectively identifying SNP1 and / or SNP2 in association with the mHTT allele in patients with HD. This study was published in Neurology Genetics in May 2020 and the manuscript is titled, "Genotyping single nucleotide polymorphisms for allele-selective therapy in Huntington's disease." In addition in October 2020, we summarized our SNP phasing methodology in a Molecular Therapy manuscript titled, "Investigational Assay for Haplotype Phasing of the Huntingtin Gene." In 2019, we entered into an agreement with Asuragen, Inc. ("Asuragen"), a molecular diagnostics company, for the development and potential commercialization of companion diagnostics for our investigational WVE-120101 and WVE-120102 allele-selective therapeutic programs in HD. We have since expanded our agreement with Asuragen to enable us to use their scalable SNP phasing technology in our clinical trial for WVE-003.

Phase 1b/2a Clinical Trials: PRECISION-HD is a global clinical program consisting of the PRECISION-HD1 and PRECISION-HD2 clinical trials. PRECISION-HD1 and PRECISION-HD2 are two parallel, multicenter, double-blind, randomized, placebo-controlled Phase 1b/2a clinical trials evaluating WVE-120101 and WVE-120102, respectively, administered intrathecally, consisting of single-ascending dose and multiple-ascending dose portions. The primary objective of these two trials is to assess the safety and tolerability of intrathecal doses of WVE-120101 and WVE-120102, respectively, in early manifest HD patients. Additional objectives include measurement of total HTT protein and mHTT protein, and exploratory pharmacokinetic, pharmacodynamic, clinical and MRI endpoints. Each trial is designed with five multi-dose cohorts (2, 4, 8, 16, and 32 mg), each with 12 patients that have Stage I or Stage II HD, ages 25-65, who have screened positively for the presence of SNP1 or SNP2. Outside of the United States, we are conducting both the single-ascending dose and multiple-ascending dose portions of the PRECISION-HD1 and PRECISION-HD2 trials. In the United States, we received approvals to proceed with the single-dose portions of both trials. However, the FDA indicated to us that we cannot progress to the multiple-ascending dose portions of these trials in the United States unless we conduct an additional preclinical study and present the resulting data to the FDA for its review. For the single-dose portion of the PRECISION-HD1 trial in the United States, escalation to our highest proposed doses is subject to the FDA's review and approval of additional monitoring plans. WVE-120101 and WVE-120102 have been granted orphan drug designation for the treatment of HD by the FDA.

PRECISION-HD2 trial: In December 2019, we announced initial clinical data from the ongoing PRECISION-HD2 trial. In an analysis comparing all patients treated with multiple intrathecal doses of WVE-120102 to placebo, a statistically significant reduction of 12.4% ($p<0.05$) in mHTT protein was observed in cerebrospinal fluid ("CSF"). An analysis to assess a dose response across treatment groups (2, 4, 8, or 16 mg) suggested a statistically significant response in mHTT reduction at the highest doses tested ($p=0.03$). WVE-120102 was generally safe and well tolerated across all cohorts. These topline data supported the addition of higher dose cohorts, and a 32 mg cohort was initiated in January 2020, which is fully enrolled. We expect to report biomarker and safety data from all cohorts of the PRECISION-HD2 trial, including all patients from the 32 mg cohort, at the end of the first quarter in 2021.

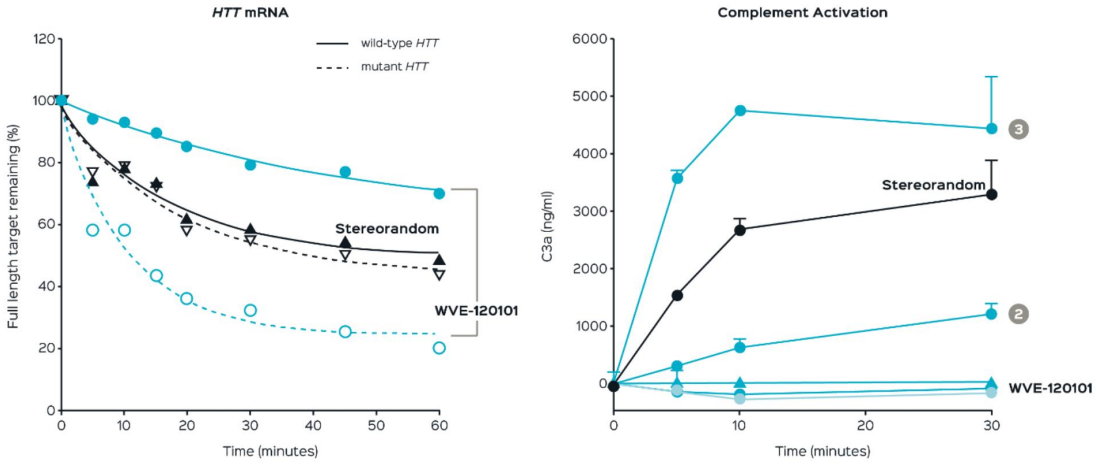
PRECISION-HD1 trial: The PRECISION-HD1 trial is fully enrolled up to the 32 mg cohort. We expect to report biomarker and safety data from all completed cohorts up to and including the 16 mg cohort at the end of the first quarter in 2021.

Open-label Extensions of PRECISION-HD1 and PRECISION-HD2: In October 2019, we initiated an open-label extension ("OLE") of the PRECISION-HD2 trial outside of the United States for patients who participated in that trial. In February 2020, we also initiated an OLE of the PRECISION-HD1 trial outside of the United States for patients who participated in that trial. Along with data from the PRECISION-HD1 and PRECISION-HD2 trials, we expect to report data from patients who have received multiple doses of 8 or 16 mg of WVE-120101 or WVE-120102 in the OLE portions of the trials at the end of the first quarter of 2021.

WVE-003 clinical trial: In December 2020, we initiated clinical development of WVE-003 with the submission of a CTA. We expect to initiate dosing in a Phase 1b/2a clinical trial of patients with HD in 2021.

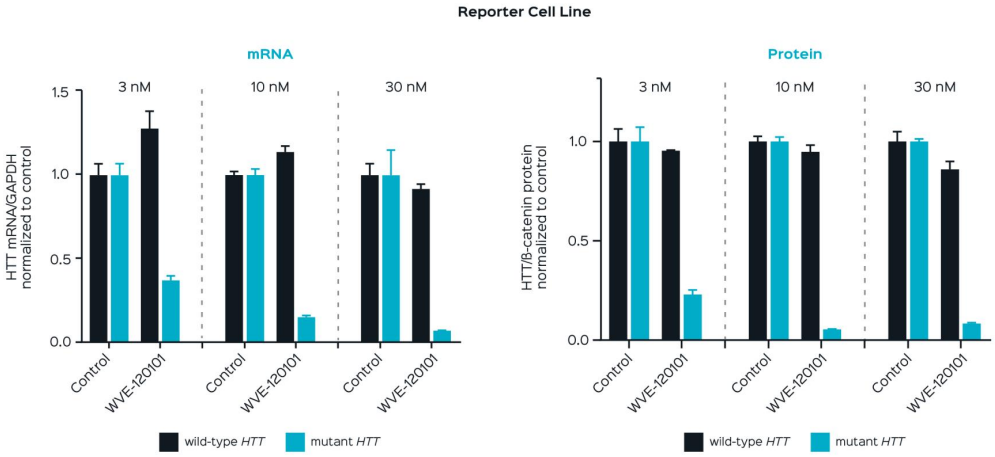
Preclinical studies

WVE-120101 and WVE-120102: In our preclinical studies, as shown below, the stereopure oligonucleotide WVE-120101 (circles) or a stereorandom oligonucleotide (triangles) were bound to wt*HTT* or m*HTT* mRNA and incubated with human RNase H (left panel). WVE-120101 produced greater knockdown of m*HTT* compared with the stereorandom oligonucleotide. In addition, WVE-120101 was selective for m*HTT* over wt*HTT*, producing relatively little knockdown of wt*HTT*. The stereorandom oligonucleotide was not selective and knocked down both wt*HTT* and m*HTT*.

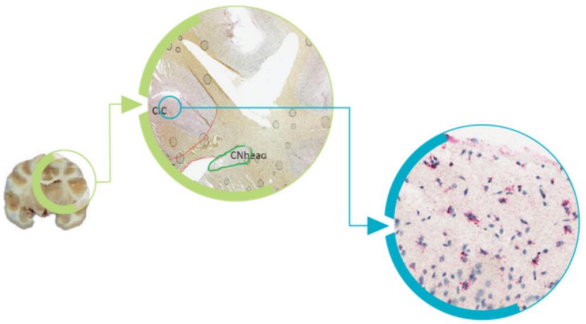


Using NHP serum, we analyzed the activation of the complement system following exposure to a panel of stereopure oligonucleotides and the parent stereorandom oligonucleotide, which were designed to target *HTT*. Each oligonucleotide was incubated at physiological temperature in NHP serum from three individual animals. Samples were removed at the indicated times, and complement activation was measured by the increase in C3a levels using the ELISA analytical method. As shown above (right panel), certain stereopure oligonucleotides and the stereorandom oligonucleotide demonstrated increased production of C3a; however, there was no production of C3a following exposure to WVE-120101, which also discriminated between wild-type and mutant *HTT*.

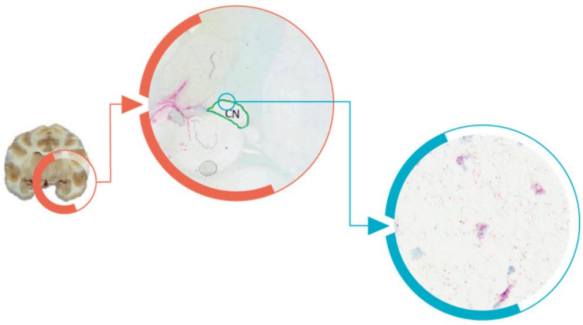
WVE-120101 was tested for potency and selectivity of knocking down m*HTT* mRNA in a cellular reporter assay. WVE-120101 targeting the m*HTT* mRNA was co-transfected into HEK293 cells with two reporter plasmids: a plasmid with V5-tagged full-length *HTT* containing the U-variant SNP1 (mutant) and a plasmid with FLAG-tagged full-length HTT containing the C-variant SNP1 (wild-type). Knockdown of m*HTT* mRNA and mHTT protein was determined by quantitative reverse transcription PCR (RT-qPCR) and western blot analysis, respectively. All results were normalized to a non-specific stereorandom oligonucleotide as a control. As shown below, WVE-120101 potently reduced m*HTT* mRNA (left panel) and mHTT protein (right panel) and exhibited significant selectivity for m*HTT* at all doses tested. This study demonstrates the ability to knock down the m*HTT* allele while leaving the wt*HTT* (healthy) allele relatively unaffected.



Following these promising preclinical experiments, we investigated distribution characteristics of WVE-120101 in NHPs. Based on our preclinical studies, we believe stereochemistry enables improved protein binding and distribution. The figure below demonstrates meaningful distribution of WVE-120101 in an NHP study. In this preclinical study, we employed an *in situ* hybridization ("ISH") ViewRNA assay. The ViewRNA assay provides us with the ability to stain oligonucleotides, allowing increased visibility and understanding of the distribution of WVE-120101 in the brain. As shown below, we found perinuclear and nuclear distribution of WVE-120101 (red) in NHP gray matter structures following intrathecal administration. The NHP ViewRNA assay demonstrated broad tissue distribution, including in the cortex and striatum. These findings are encouraging as we believe that distribution and penetration into several areas of the brain will be critical for the successful treatment of HD.



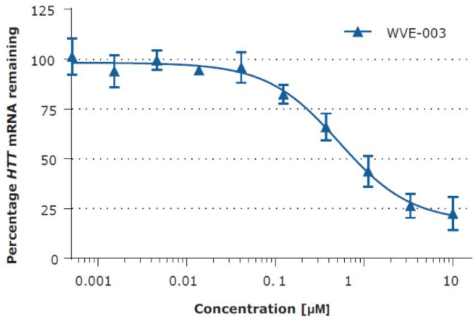
Red dots are WVE-120101 oligonucleotide.
Arrow points to nuclear and perinuclear distribution of WVE- 120101 in cingulate cortex



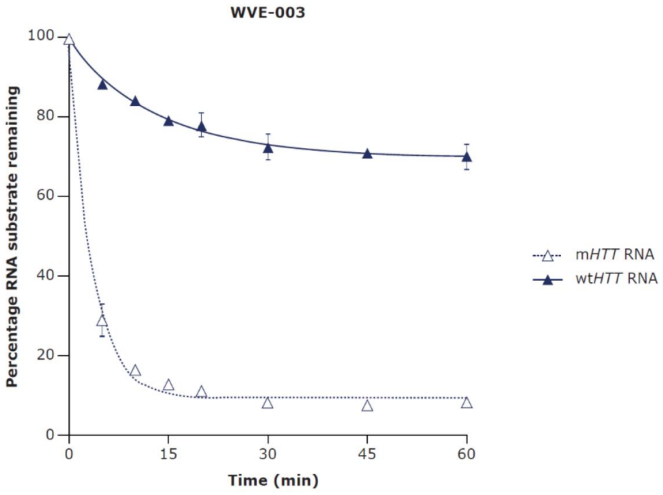
Red dots are WVE-120102 oligonucleotide.
Arrow points to nuclear and perinuclear distribution of WVE-120102 in caudate nucleus

Preclinical studies on WVE-120102 showed similar results with regard to RNase H-mediated activity, m*HTT* allele specificity, and distribution in NHP brain.

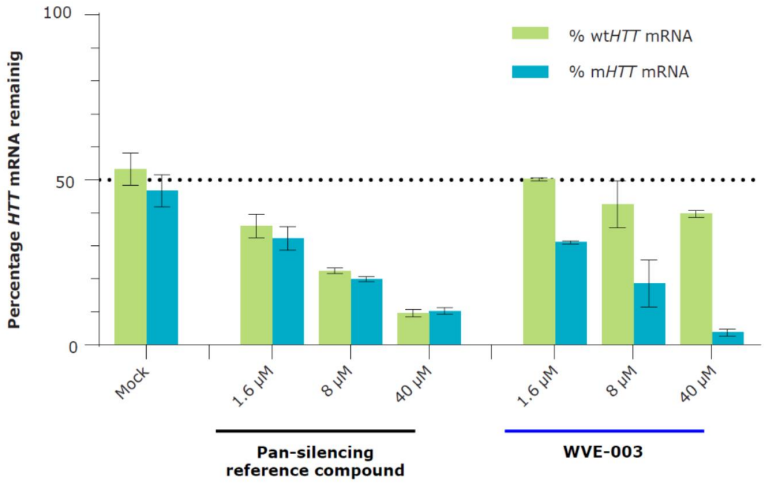
WVE-003: Using PRISM and our PN chemistry backbone modifications, we have designed WVE-003, an allele-selective stereopure oligonucleotide that specifically targets mHTT SNP3 on the mHTT mRNA while leaving wtHTT mRNA relatively intact in vitro. WVE-003 showed potent knockdown of mHTT mRNA in a preclinical study using induced pluripotent stem cell (iPSC)-derived motor neurons.



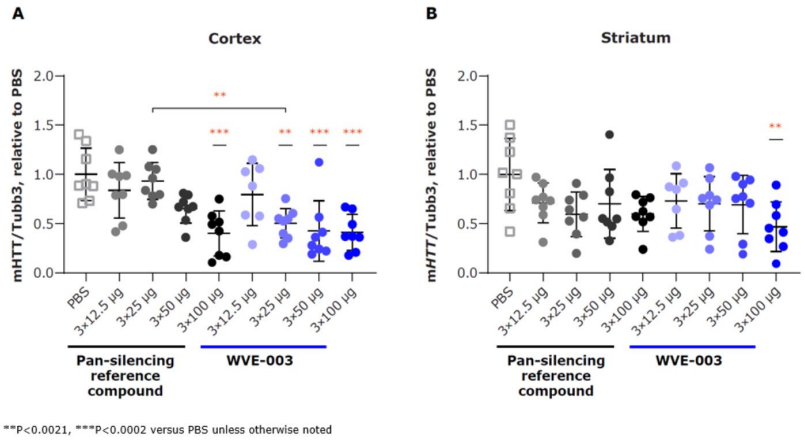
WVE-003 promoted RNase H–mediated degradation of mHTT RNA while sparing wtHTT RNA in a biochemical assay.



We further demonstrated selectivity of WVE-003 in assays performed in induced pluripotent stem cell (iPSC) neurons from patients with HD that are heterozygous for SNP3. These cells are amenable to the free-uptake delivery method that is an integral part of PRISM. WVE-003 selectively silences the mutant transcript while largely sparing the wild-type transcript. By comparison, the pan-silencing active comparator silences both mutant and wild-type HTT transcripts.

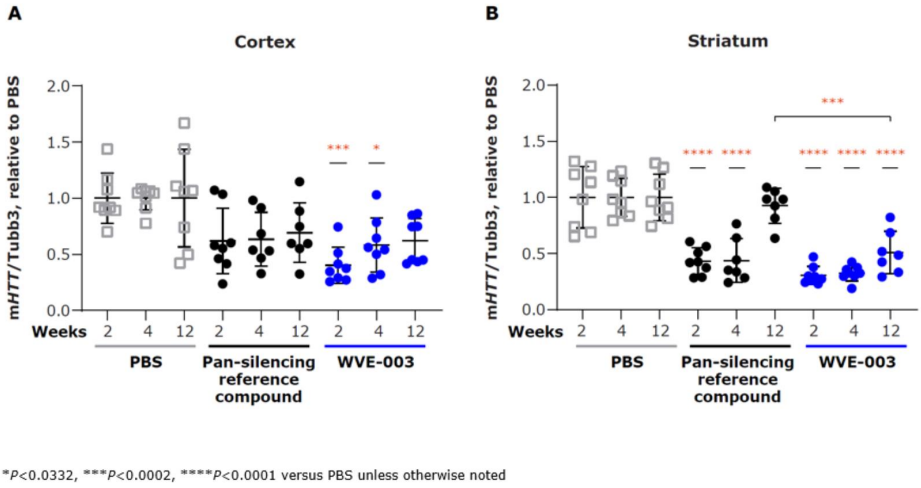


We next tested our SNP3 compounds *in vivo* in a BACHD model for Huntington's disease. This model expresses a mutant version of the human HTT gene. The model is homozygous for SNP3, so it is not suitable for assessing selectivity, but enables assessment of target engagement *in vivo*. Importantly, the model expresses multiple copies of the transgene; however, not all of the copies contain SNP3, so our SNP3 compounds cannot silence all the mHTT transcripts in these mice. After administration, WVE-003 showed significant mHTT mRNA knockdown compared with phosphate-buffered saline (PBS) at the highest concentration tested in the striatum and all but the lowest concentration tested in the cortex. WVE-003 showed comparable reduction of mHTT mRNA to that of the pan-silencing oligonucleotide, despite having fewer targets in these mice.



**P<0.0021, ***P<0.0002 versus PBS unless otherwise noted

In the cortex of BACHD mice, WVE-003 showed significant mHTT knockdown compared PBS through week 4. In the striatum, WVE-003 led to significant and durable mHTT knockdown that was sustained for 12 weeks, compared with PBS. WVE-003 led to significantly more knockdown than the pan-silencing reference compound at week 12. Since most but not all of the transgenes in this model contain SNP3, our SNP3 compounds are handicapped slightly versus the pan-silencing active comparator.



*P<0.0332, ***P<0.0002, ****P<0.0001 versus PBS unless otherwise noted

Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

Hexanucleotide G4C2 expansions found in the *C9orf72* gene are one of the most common genetic causes of the sporadic and inherited forms of Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD). Some patients exhibit characteristics of both ALS and FTD, indicating that these diseases form part of a continuum of neurological disease with some overlap in symptoms between them.

ALS Background and Market Opportunity

ALS is a neurodegenerative disease characterized by the progression and degeneration of motor neurons in the brain and spinal cord. Diagnosis may take up to 12 months and is made clinically by assessing the signs of upper and lower motor neuron degeneration in the same region of the body. Patients initially present with limb-onset disease (approximately 70% of patients), bulbar-onset disease (approximately 25% of patients) or with initial trunk or respiratory involvement (approximately 5% of patients). Age of onset is generally in the mid-to-late 50's, and median survival is three years; however, up to 24% of patients survive for five to ten years. Survival in patients with *C9orf72* ALS may be shorter than in patients with sporadic ALS.

In the United States and Europe combined, there are approximately three to five ALS patients per 100,000 people. This translates to approximately 13,000 diagnosed patients in the United States, although the total prevalence may be around 20,000 people in the United States. There are one or two newly diagnosed cases of ALS per year, per 100,000 people in the United States and Europe combined, resulting in approximately 5,000 newly diagnosed patients in the United States each year. While the majority of ALS cases are sporadic, approximately 10% of cases are found to be familial in nature. The *C9orf72* gene mutation is currently the most common demonstrated mutation related to ALS and is present in approximately 40% of familial ALS and 8-10% of sporadic ALS patients.

ALS Current Treatments

There is significant unmet need for the treatment of ALS. Two medicines are currently approved in the United States for the treatment of ALS. Rilutek (riluzole), an inhibitor of glutamate release, was approved in 1995 for the treatment of patients with ALS. It was demonstrated to extend survival by three to six months. Radicava (edaravone) was approved in 2017 for the treatment of ALS. Administration of edaravone resulted in a significantly smaller decline in the ALS Functional Ration Scale-Revised (ALSFRS-R) through six months of treatment as compared to placebo.

FTD Background and Market Opportunity

FTD is a neurodegenerative disorder of the frontal and anterior temporal lobes of the brain. It is characterized by changes in personality, cognition (e.g., language impairment and executive dysfunction), and behavior (e.g., disinhibition, apathy and compulsivity). Diagnostic criteria categorize FTD into either the behavioral variant (approximately 60% of patients) or speech/language variant (approximately 40% of patients) based on the primary symptom observed at presentation; however, FTD results in dementia in all patients. The majority of FTD associated with the G4C2 expansion in the *C9orf72* gene is categorized as the behavioral variant. FTD frequently has an onset in mid-life, and death typically occurs within three to 14 years of onset. FTD is the second most common form of early-onset dementia in people under the age of 65, after AD.

In FTD, the *C9orf72* gene mutations appear in approximately 38% of familial cases and approximately 6% of sporadic cases. FTD affects approximately 55,000 people in the United States, of which 10 – 50% are familial cases and 50 – 90% are sporadic cases.

FTD Current Treatments

There are currently no disease-modifying therapies approved for the treatment of FTD. Treatment to date has involved use of medications for symptomatic management.

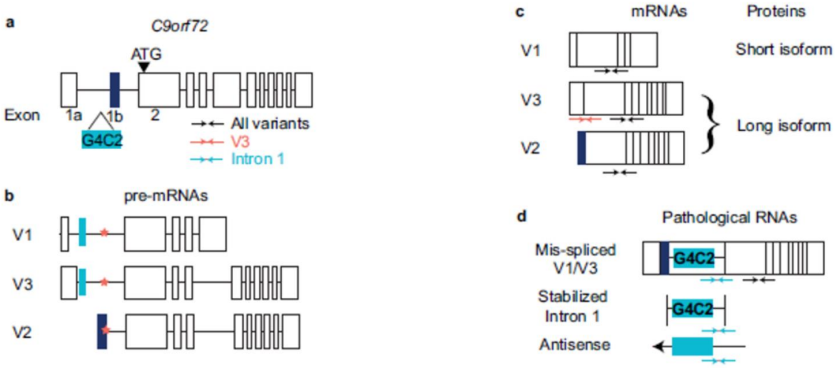
Our Program

In ALS and FTD, we are advancing WVE-004, which preferentially targets the transcripts containing the hexanucleotide G4C2 expansion in the *C9orf72* gene. WVE-004 is designed to minimize the impact on normal C9orf72 protein in patients, thereby reducing potential on-target risk. *In vitro*, WVE-004 potently and selectively reduced V3 transcripts in iPSC-derived motor neurons, which were derived from a patient carrying a C9orf72-repeat expansion. In C9 BAC transgenic mice, WVE-004 led to substantial reductions in repeat-containing C9orf72 transcripts and dipeptide repeat (DPR) proteins that are sustained for at least six months, without disrupting total protein expression.

WVE-004 clinical trial: In December 2020, we initiated clinical development of WVE-004 with the submission of a CTA. We expect to initiate dosing in a Phase 1b/2a clinical trial of both patients with C9-ALS and patients with C9-FTD in 2021.

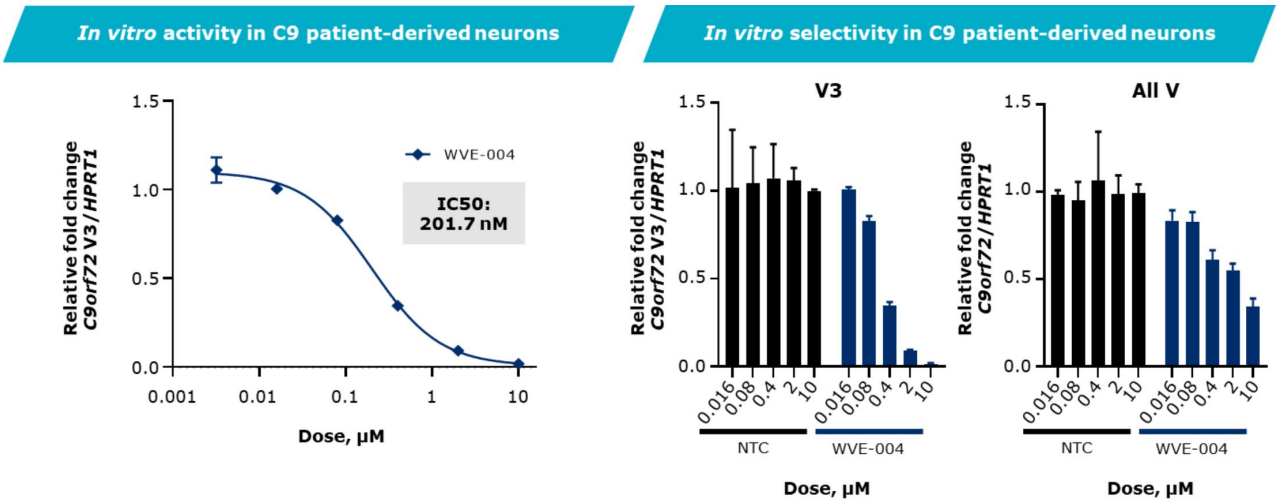
Expansion of the G4C2 repeat alters the normal expression of the *C9orf72* gene and causes the production of repeat-containing RNAs. These RNAs accumulate in cellular nuclei in the form of RNA foci and can be translated into DPR proteins. Neuronal degeneration associated with the expression of the repeat expansion is hypothesized to arise either from a toxic loss-of-function mechanism due to a reduction in C9orf72 protein or a toxic RNA gain-of-function mechanism through the accumulation of RNA foci and/or DPRs in the brain and spinal cord.

In our *Nature Communications* paper (Liu, Y et al. Nat Comms. 2021), we report the discovery of a new targeting sequence that is common to all *C9orf72* transcripts but enables preferential knockdown of repeat-containing transcripts in multiples models and C9BAC transgenic mice. Wild-type *C9orf72* alleles produce three mRNA transcripts: variant 1 (V1), variant (V2), and variant (V3). We apply our platform to generate stereopure oligonucleotides that target a sequence at the exon 1b-intron 1 junction, termed Splice Site-1b ("SS1b"), that is common to all *C9orf72* transcripts (shown below in "b", pre-mRNAs corresponding to V1-V3 are illustrated; the coral star indicates SS1b). In multiple in vitro model systems, an unoptimized stereopure oligonucleotide yields preferential knockdown of exon1a-containing transcripts. The *Nature Communications* paper describes our work to identify and validate the targeting site to achieve variant-selective knockdown of expansion-containing C9orf72 transcripts. The publication highlights the foundational work that led to the development of our clinical candidate.

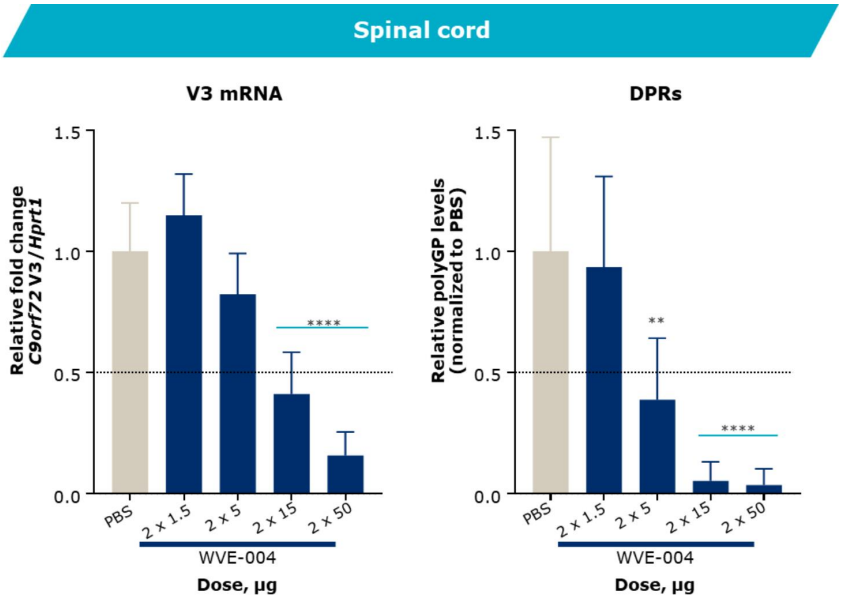


By targeting the V1 and V3 mRNA transcripts that contain the G4C2 expansion and sparing V2 transcripts and healthy C9orf72 protein, WVE-004 has the potential to reduce both RNA-based and protein-based toxicity, thereby impacting the disease course and slowing the progression of ALS or FTD.

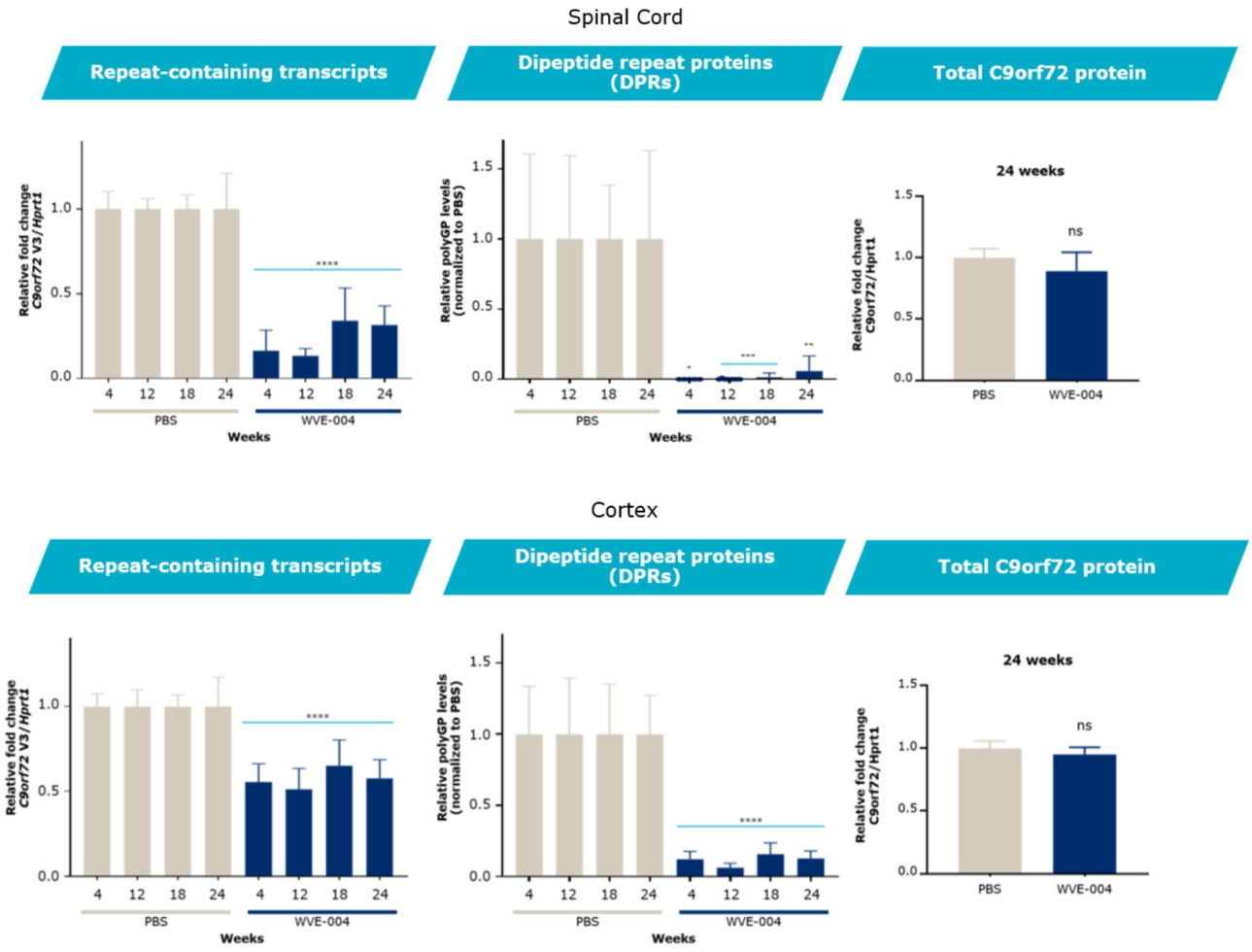
In vitro, WVE-004 potently and selectively reduced V3 transcripts in iPSC-derived motor neurons, which were derived from a patient carrying a *C9orf72* repeat expansion.



WVE-004 led to dose-dependent knockdown of V3 transcripts and DPRs in mouse spinal cord tissue. In the transgenic model, mice express the human *C9orf72* repeat-containing gene from a bacterial artificial chromosome ("BAC") insertion. We observed qualitatively similar dose-dependent knockdown of V3 transcripts and the polyGP DPR protein in mouse cortex tissue (data not shown).



In C9 BAC transgenic mice, WVE-004 led to substantial reductions in repeat-containing *C9orf72* transcripts and dipeptide repeat (DPR) proteins that are sustained for at least six months, without disrupting total protein expression.



Spinocerebellar ataxia 3

Background and Market Opportunity

SCA3 is a rare, hereditary (autosomal dominant) progressive neurodegenerative disorder that results in a lack of muscle control and coordination of the upper and lower extremities. Signs and symptoms of SCA3 may begin between childhood and late adulthood, and they vary greatly. Symptoms may include progressive clumsiness in the arms and legs, spasticity, difficulty with gait, and impaired speaking, swallowing and eye movements. Symptoms of the disease worsen over time, eventually leading to paralysis. Some patients with SCA3 develop dystonia or symptoms similar to those of PD, including twitching of the face or tongue, and nerve damage (neuropathy). Life expectancy ranges from the mid-30s in the more severe forms, to a nearly normal life expectancy for those with milder forms of the disease.

SCA3 is caused by a CAG-repeat expansion in the *ATXN3* gene, resulting in an abnormally long polyglutamine stretch in the encoded ataxin-3 protein. Mutant ataxin-3 protein is thought to cause widespread neuronal loss in the brain and spinal cord, likely through a toxic gain-of-function mechanism. SCA3 is the most common dominantly inherited form of ataxia. The prevalence of SCA3 is believed to be one to two cases in 100,000 people with significant geographic and ethnic variations.

Current Treatments

There are currently no disease-modifying therapies approved for treatment of SCA3. Treatment to date has involved the use of medications for symptomatic management.

Our Program

In SCA3, we are continuing to advance our program targeting ATXN3.

Duchenne Muscular Dystrophy

Background and Market Opportunity

DMD is a rare, genetic progressive neuromuscular disorder caused by mutations in the dystrophin gene on the X chromosome that affects approximately one in 5,000 newborn boys around the world (approximately 20,000 new cases annually). The dystrophin protein is part of a protein complex called the dystrophin-associated protein complex that acts as an anchor, connecting each muscle cell's structural framework with a lattice of proteins and other molecules outside the cell through the muscle cell membrane. The dystrophin-associated protein complex protects the muscle from injury during contraction and relaxation. Patients with DMD typically develop muscle weakness in the early years of life and become wheelchair-bound in their early teens. As the disease progresses, DMD patients typically develop respiratory, orthopedic and cardiac complications. Cardiomyopathy and breathing difficulties usually begin by the age of 20, and few individuals with DMD live beyond their thirties.

Current Treatments

While there are approved therapies for DMD, there is no cure, and there continues to be significant unmet medical need. In most countries, corticosteroids are the standard drug therapy, which slows the progression of muscle weakness and delays loss of ambulation by two to three years. In February 2017, the FDA approved Emflaza (deflazacort), the first corticosteroid approved as a treatment in the United States for DMD patients older than five years of age.

In 2016, Sarepta Therapeutics' Exondys 51™ *(*eteplirsen) received accelerated approval in the United States for the treatment of patients with DMD, who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping. In 2019, Sarepta Therapeutics' Vyondys 53™ (golodirsen) received accelerated approval in the United States for the treatment of patients with DMD who have a confirmed mutation of the dystrophin gene amenable to exon 53 skipping. Additionally, in 2020, the FDA granted accelerated approval to NS Pharma's Viltepso™ (viltolarsen) for DMD patients with a mutation amenable to exon 53 skipping. NS Pharma has also received Marketing Authorization for Viltepso in Japan. According to U.S. accelerated approval guidelines, no clinical benefit needs to be established at the time of FDA approval, and no clinical benefit of has yet been established for eteplirsen, golodirsen, or vitolarsen. Thus, in accordance with the U.S. accelerated approval regulations, the FDA is requiring Sarepta to conduct clinical trials to verify and describe the clinical benefit of eteplirsen, golodirsen and is requiring NS Pharma to conduct a clinical trial to verify and describe the clinical benefit of viltolarsen. If any of these confirmatory trials fail to verify clinical benefit, the FDA could initiate proceedings to withdraw approval of the respective drug.

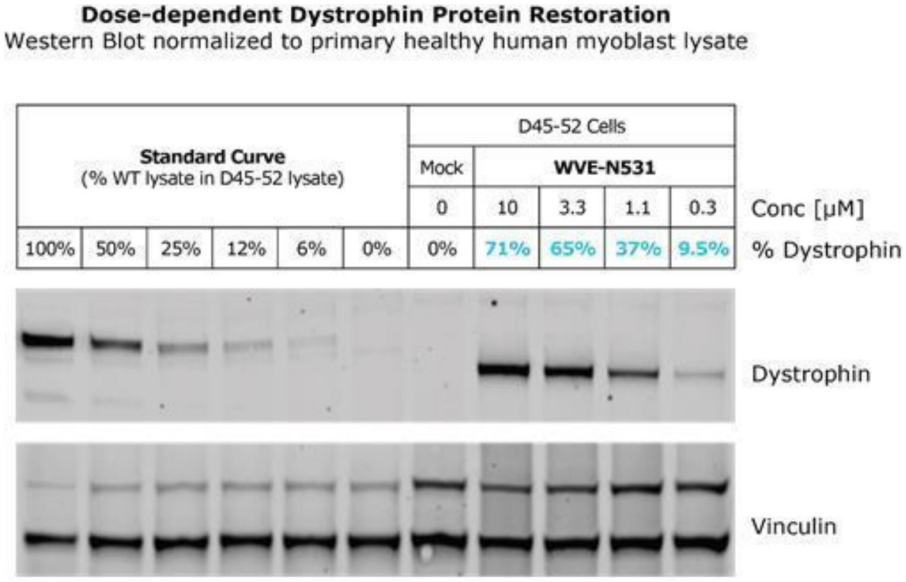
In 2014, PTC Therapeutics' Translarna™ (ataluren) was the first disease-modifying treatment to receive conditional approval by the EMA for the treatment of ambulatory DMD patients over 5 years of age who have a nonsense mutation (12% of DMD cases) in the dystrophin gene. In 2016, the EMA did not allow ataluren to convert to full marketing authorization, rather it granted a renewal of the conditional approval. In 2018, EMA expanded the conditional approval for Translarna to include treatment of ambulatory DMD patients ≤2 years of age who have a nonsense mutation in the dystrophin gene. In June 2020, the EMA removed a statement from the SmPC for Translarna that "efficacy has not been demonstrated in non-ambulatory patients."

Our Program

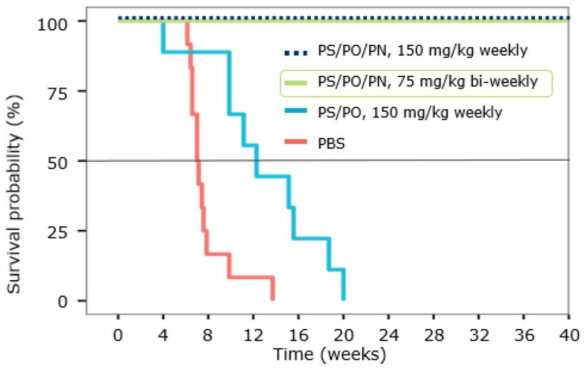
In DMD, we are advancing WVE-N531, which is designed to target exon 53 within the dystrophin gene. WVE-N531 is designed to cause the cellular splicing machinery to skip over this exon during pre-mRNA processing, which restores the dystrophin mRNA reading frame and enables production of truncated, but functional dystrophin protein. Exon-skipping produces dystrophin from the endogenous dystrophin gene (not micro or mini dystrophin expressed from a vector), under the control of native gene-regulatory elements, resulting in normal temporospatial expression. WVE-N531 will be our first splicing candidate incorporating PN backbone chemistry modifications to be assessed in the clinic. We expect to submit a CTA for WVE-N531 by the end of the first quarter in 2021.

In vitro, WVE-N531 induced dose-dependent exon 53 skipping up to 49% and dystrophin protein restoration up to 71% in DMD patient-derived myoblasts carrying a deletion of exons 45-52. In these experiments, cells were exposed to WVE-N531 at 0.1 μM-10 μM under gymnotic conditions. After four days of oligonucleotide treatment, efficiency at skipping exon 53 was determined by

quantitative RT-PCR. After six days of oligonucleotide treatment, protein lysate was analyzed by western blot for dystrophin protein expression.



To understand the effects of PN backbone chemistry modifications *in vivo*, we conducted a study in a double-knockout or "dKO" mouse model, which has a mutation in exon 23 leading to a lack of dystrophin, as well as a mutation leading to a lack of utrophin. We compared the effects of a PS/PO-containing molecule dosed at 150 mg/kg weekly to a PN-containing compound dosed at the same level, a PN-containing compound at 75 mg/kg every other week and a control group dosed with PBS. Other than the placement of the three PN backbone linkages, these molecules have the same sequence and chemistry. There is a significant increase in survival in those animals treated with PN containing compounds as compared with the other treatment groups. As shown in the figure below on the left, both cohorts of mice receiving the PN-containing molecules (shown in dark blue and light green) had 100% survival at the time of study termination, with a median age of approximately 40 weeks. By comparison, the median survival for the mice receiving the PS/PO-containing molecule dosed at 150 mg/kg weekly was approximately 12 weeks and the dKO control animals that received PBS had a median survival of approximately seven weeks.



Note: Untreated, age-matched mdx mice had 100% survival at study termination [not shown]

Alpha-1 Antitrypsin Deficiency

Background and Market Opportunity

We are leveraging our ADAR editing platform capability to develop a potentially novel treatment for alpha-1 antitrypsin deficiency ("AATD"). AATD is a rare, inherited genetic disorder that is commonly caused by a G-to-A point mutation in the Z allele of the *SERPINA1* gene. This mutation leads to misfolding and aggregation of alpha-1 antitrypsin ("AAT") protein in hepatocytes and a lack of functional AAT in the lungs. People with AATD typically exhibit progressive lung damage, liver damage or both, leading to frequent hospitalizations and potentially terminal lung disease and/or liver disease. While the few approved therapies for AATD modestly increase circulating levels of AAT in those with the lung pathology, there are no approved therapies to address the liver pathology. Approximately 200,000 people in the United States and Europe are homozygous for the Z allele, which is the most common form of severe disease.

Current Treatments

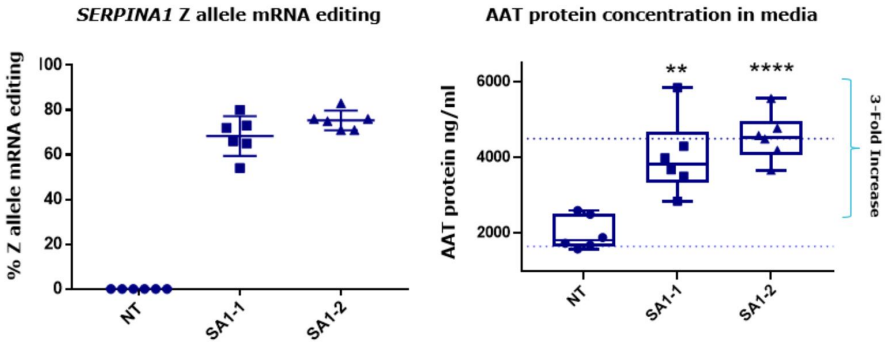
There are five treatments currently approved in the United States for chronic augmentation and maintenance therapy in adults with emphysema due to congenital deficiency of alpha1-proteinase inhibitor (Alpha1-PI). Per FDA labeling for each, the effect of augmentation therapy with any alpha1-proteinase inhibitor on pulmonary exacerbations and on the progression of emphysema in Alpha1-PI deficiency has not been demonstrated in randomized, controlled clinical trials. Patients with AATD can also be treated with therapies used in other lung diseases including bronchodilators to open airways and corticosteroids to reduce chronic inflammation common in the lungs of AATD patients.

There are currently no approved therapies to prevent the accumulation of the mis-folded AAT protein in the liver. Treatments are available to help deal with intestinal bleeding, fluid in the abdomen, nutritional issues and other complications from scarring of the liver, but ultimately many patients will progress towards requiring a liver transplant.

Our Program

In November 2020, we announced that our first ADAR editing program would be for AATD. Our novel RNA editing platform capability uses endogenous ADAR enzymes of A-to-I (G) base editing oligonucleotides, making this a potentially best-in-class modality for correcting the G-to-A disease-causing mutation in mRNA coded by the *SERPINA1* Z allele. By correcting the single RNA base mutation, ADAR editing may provide an ideal approach for increasing circulating levels of wild-type AAT protein and reducing aggregation in the liver, thus simultaneously addressing both the lung and liver manifestations of the disease.

In a primary hepatocyte *SERPINA1* Z allele cell model, we demonstrated that editing the Z allele mRNA restored protein secretion from hepatocytes, as shown in the figure below. We observed upwards of 60% correction of the Z allele mRNA back to wild-type transcript (left), which prevented protein misfolding and increases secretion of editing AAT protein from hepatocytes (right). Edited, wild-type AAT protein was confirmed to be wild-type by mass spectrometry and the function of secreted, edited AAT protein was confirmed by neutrophil elastase inhibition assay. We expect to deliver *in vivo* data supporting the continued development of our AATD program in the first half of 2021.



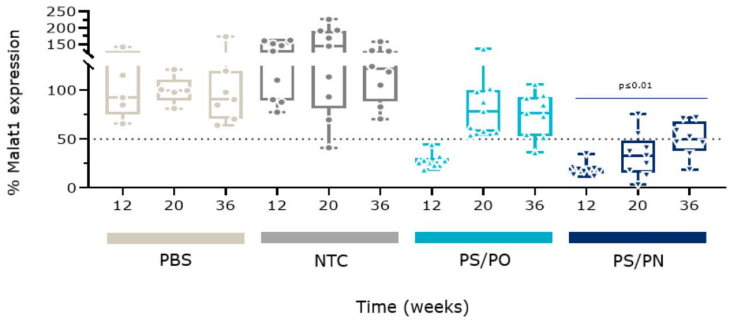
Ophthalmology

In ophthalmology, we have generated *in vitro*, *ex vivo* and *in vivo* data in preclinical studies that support the potential of our stereopure oligonucleotides for the treatment of rare, inherited eye diseases. Our preclinical data demonstrate that a single intravitreal injection of stereopure oligonucleotide in the eye of non-human primates ("NHPs") resulted in greater than 95% knockdown of a target RNA in the retina for at least 4 months. Based on these data, our goal is to design candidates that could achieve a therapeutic effect with only two doses per year. Our pipeline includes two preclinical programs: Usher syndrome type 2A ("USH2A") and retinitis pigmentosa due to a P23H mutation in the *RHO* gene ("RhoP23H"). In September 2020, we presented *in vitro*, *ex vivo*, *and in vivo* preclinical data on our USH2A program, which is designed to promote *USH2A* exon 13 skipping, and we presented *in vitro* and *in vivo* data on our RhoP23H program, which is designed to selectively silence RhoP23H transcripts. We also presented results from our first achievement of ADAR editing in NHP retina *ex vivo* using stereopure oligonucleotides.

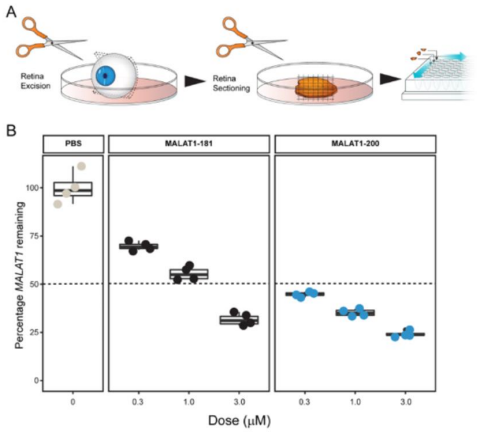
We believe PRISM affords us a unique opportunity to address these challenging inherited retinal diseases. Oligonucleotides developed based on PRISM demonstrate superior potency and durability as compared to stereorandom oligonucleotides and are optimized to minimize immune activity and can yield selective activity against closely related sequences.

We have demonstrated with preclinical, proof of concept studies with oligonucleotides targeting *Malat1* that our stereopure compounds exhibit these desirable properties specifically in the eye. These studies (see below) supported our decision to develop therapeutic candidates with the potential to be potently and durably active, which would allow for less frequent administration via intravitreal ("IVT") injection and would give us an advantage over molecules delivered via subretinal injection or that are less potent and require frequent IVT injection.

Our discovery research has tested the hypothesis that controlling the chirality of PS linkages in the backbones of oligonucleotides will provide a benefit in potency, tissue distribution and duration of effect in the eye. In these studies, we have employed *Malat1* as a surrogate target. Previously, we generated stereopure compounds targeting *Malat1*, a nuclear-enriched, long non-coding RNA and evaluated them *in vitro* in iCell neurons under gymnotic conditions. Our best-performing compounds exhibited IC_{50} values approximately 24-fold lower than those of stereorandom oligonucleotides of comparable sequence and chemistry. PRISM optimization with PN chemistry resulted in identification of compounds that exhibit a further 8-fold shift in IC_{50} *in vitro* under gymnotic conditions. We then evaluated the optimized stereopure oligonucleotides *in vivo* following a single IVT injection (50 µg) in the mouse eye. We assessed expression of *Malat1* RNA by qPCR over a nine-month period. In the posterior of the eye (retina, choroid, sclera), a single 50 µg IVT injection of stereopure ASO with PN linkages (shown in navy) led to 50% knockdown of *Malat1* that persisted for up to nine months (shown in the figure below). The incorporation of a few PN linkages resulted in substantial durability benefits.



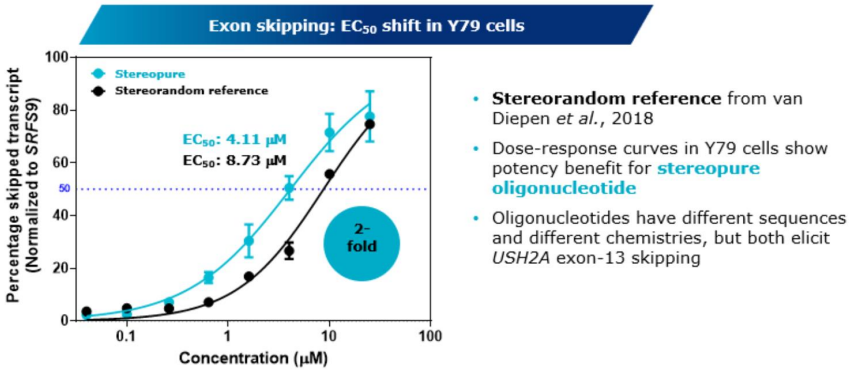
In our *Translational vision science & technology* paper (Byrne M, et al. Trans Vis Sci Tech. 2021;10(1):23), we describe an optimized stereopure antisense oligonucleotide, MALAT1-200, that shows enhanced potency, efficacy, and durability of MALAT1 RNA depletion in the eye compared with its stereorandom counterpart, MALAT1-181, in mouse and NHP eyes via IVT injection (see section 'PRISM: Our proprietary discovery and drug development platform'). After validating the efficacy and durability of the stereopure oligonucleotide in NHP eyes, we tested its activity in ex vivo cultures of human retinal tissue from donor eyes (as shown below in "A"). Retinal tissue samples were treated with vehicle, stereorandom MALAT1-181 (0.3, 1, and 3 µM), or stereopure oligonucleotide MALAT1- 200 (0.3, 1, and 3 µM) under gymnotic conditions for 48 hours. Overall, there was an effect of treatment independent of dose ($P < 0.001$), an effect of dose independent of treatment ($P < 0.001$), and an effect of treatment at each dose ($P < 0.001$, three-way ANOVA). At 0.3- and 1-µM doses, stereopure oligonucleotide was more active than stereorandom oligonucleotide, leading to a significantly larger decrease in the percentage of remaining MALAT1 RNA expression (0.3 µM: 44.7% vs. 60.7%, $P < 0.001$; 1 µM: 35.3% vs. 55.4%, $P < 0.001$). In addition, 0.3 µM of stereopure oligonucleotide led to a significantly larger decrease in the percentage of MALAT1 RNA expression versus 1 µM of stereorandom oligonucleotide ($P < 0.05$). At 1 µM, activity of the stereopure oligonucleotide matched activity observed with 3 µM of stereorandom oligonucleotide ($P > 0.05$), indicating the potency and efficacy benefit with stereopure oligonucleotide detected in mice may translate to humans (as shown below in "B").



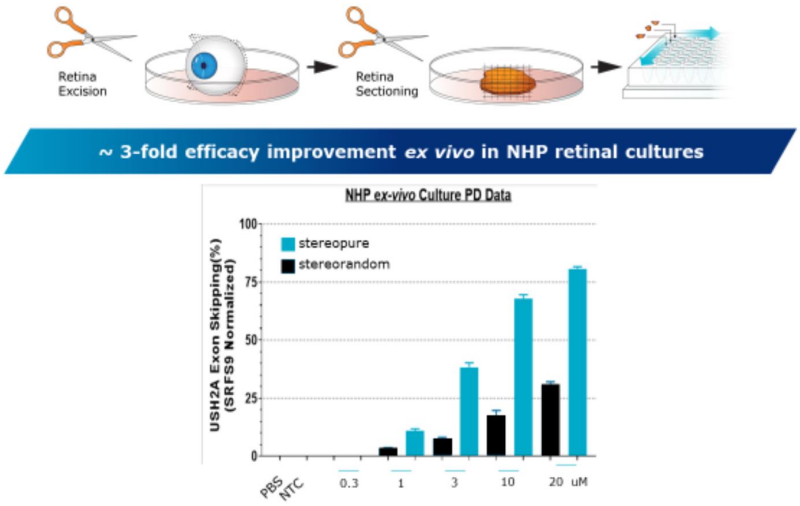
These preclinical studies support the hypothesis that stereopure compounds can be designed to increase the potency, tissue distribution and duration of effect in the eye compared with stereorandom oligonucleotides.

USH2A program: Usher syndrome type 2A is an autosomal recessive disease characterized by hearing loss at birth and progressive vision loss beginning in adolescence or adulthood. It is commonly caused by a mutation that introduces a stop codon and prevents translation of usherin protein, leading to progressive degeneration of photoreceptors. Antisense oligonucleotides that preferentially promote exon skipping may restore production of functional usherin protein and potentially confer therapeutic benefit in patients.

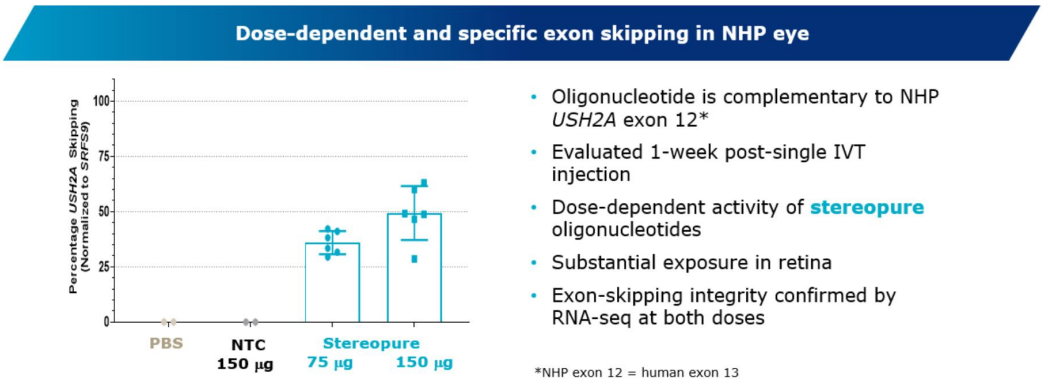
In 2020, at TIDES: Oligonucleotides and Peptide Therapeutics, we presented our preclinical USH2A data. To evaluate potency, a stereopure antisense oligonucleotide targeting USH2A (Compound 1) and a stereorandom reference antisense oligonucleotide (ASO) described in WO2018055134A1 were added to Y79 cells under free-uptake conditions, and exon-skipping was evaluated by qPCR.



As shown above, a stereopure antisense oligonucleotide (light blue) induced dose-dependent *USH2A* exon skipping that was 2-fold more potent than a stereorandom reference ASO under gymnotic conditions in Y79 cells.



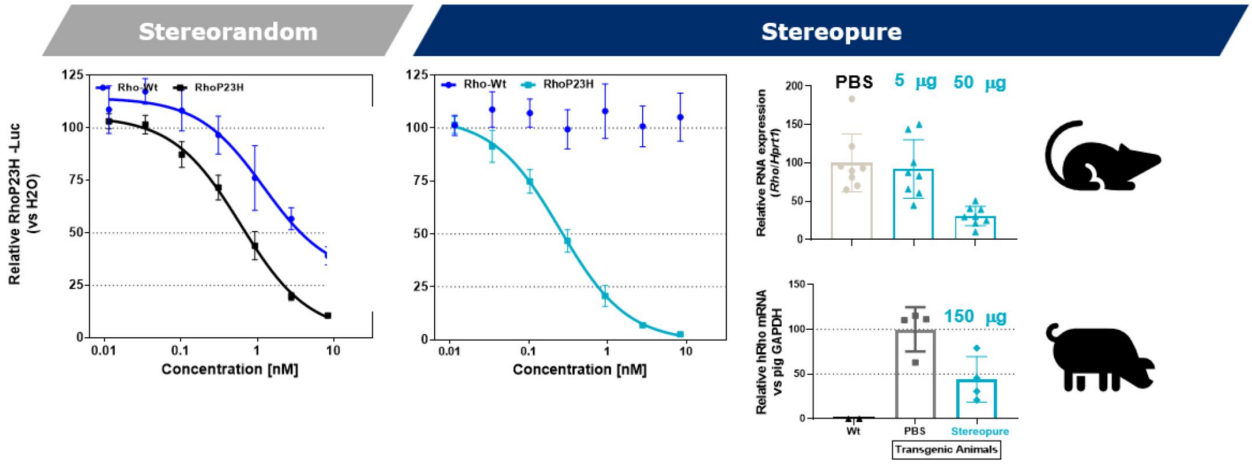
Ex vivo approaches enable us to investigate the activity of stereopure antisense oligonucleotides under gymnotic conditions in NHP eyes and bridge the gap between *in vitro* and *in vivo* studies. As shown above, a stereopure oligonucleotide (light blue) induced dose-dependent *USH2A* exon skipping in the NHP retina *ex vivo* under gymnotic conditions 48 hours after treatment.



Moving *in vivo*, as shown above, a stereopure oligonucleotide elicited dose-dependent exon-skipping in NHP retina.

Retinitis pigmentosa (RP) program: Retinitis pigmentosa is a group of rare, genetic eye disorders resulting in progressive photoreceptor cell death and gradual loss of function. Currently, there is no cure for this condition. Approximately 10% of U.S. autosomal dominant RP cases are caused by the P23H mutation in the rhodopsin gene (RHO). Mutant P23H rhodopsin protein is thought to misfold and co-aggregate with wild-type rhodopsin, resulting in a gain-of-function or dominant negative effect in rod photoreceptor cells.

A luciferase reporter assay was developed to evaluate the ability to selectively reduce mutant RhoP23H transcript while maintaining wild-type transcript. An allele-selective stereopure sequence identified with PRISM as well as a stereorandom sequence described in WO2016138353A1 and luciferase reporter plasmids (wild-type and mutant rhodopsin) are transfected into Cos7 cells. 48-hours later, cells were harvested, and relative luminescence was measured.



As shown above, dose-dependent reduction of mutant and wild-type Rhodopsin transcripts resulted from treatment with the reference stereorandom molecule (left side figure). However, dose-dependent reduction of only the mutant RhoP23H transcript occurred following treatment with our stereopure, allele-selective sequence (middle figure). In a surrogate *in vivo* system (top right figure), stereopure oligonucleotides targeting the mouse P23H mutation reduced the target in a dose dependent manner 1 week post single IVT injection providing proof of concept data for targeting this mutation *in vivo*. Utilizing a pig model carrying the human P23H mutation, our allele-selective stereopure oligonucleotide reduced human P23H RNA expression 2-weeks post single IVT.

Licensing Arrangements and Research Collaborations

Our business strategy is to develop and commercialize a broad pipeline of novel nucleic acid therapies. As part of this strategy, we have entered into, and may enter into new partnership and collaboration agreements as a means of advancing our own nucleic acid therapeutic programs, investing in third-party technologies to further strengthen PRISM and leveraging external partnerships to extend the reach of PRISM into therapeutic areas where our platform demonstrates a competitive advantage.

Our Partnerships

Takeda

In February 2018, Wave Life Sciences USA, Inc. (“Wave USA”) and Wave Life Sciences UK Limited (“Wave UK”) entered into a global strategic collaboration (the “Takeda Collaboration”) with Takeda Pharmaceutical Company Limited (“Takeda”), pursuant to which Wave USA, Wave UK and Takeda agreed to collaborate on the research, development and commercialization of oligonucleotide therapeutics for disorders of the Central Nervous System (“CNS”). The Takeda Collaboration provides Wave with at least $230.0 million in committed cash and Takeda with the option to co-develop and co-commercialize Wave’s CNS development programs in (1) Huntington’s disease (“HD”); (2) amyotrophic lateral sclerosis (“ALS”) and frontotemporal dementia (“FTD”); and (3) Wave’s discovery-stage program targeting *ATXN3* for the treatment of spinocerebellar ataxia 3 (“SCA3”) (collectively, “Category 1 Programs”), which we will have the right to co-commercialize in the United States. In addition, Takeda will have the right to exclusively license multiple preclinical programs for CNS disorders, including Alzheimer’s disease and Parkinson’s disease (collectively, “Category 2 Programs”). In April 2018, the Takeda Collaboration became effective and Takeda paid Wave $110.0 million as an upfront payment. Takeda also agreed to fund Wave’s research and preclinical activities in the amount of $60.0 million during the four-year research term and to reimburse Wave for any collaboration-budgeted research and preclinical expenses incurred by Wave that exceed that amount.

Simultaneously with Wave USA and Wave UK’s entry into the collaboration and license agreement with Takeda (the “Takeda Collaboration Agreement”), the Company entered into a share purchase agreement with Takeda (the “Takeda Equity Agreement,” and together with the Takeda Collaboration Agreement, the “Takeda Agreements”) pursuant to which it agreed to sell to Takeda 1,096,892 of its ordinary shares at a purchase price of $54.70 per share. In April 2018, the Company closed the Takeda Equity Agreement and

received aggregate cash proceeds of $60.0 million. The shares purchased by Takeda are subject to lock-up and standstill restrictions and carry certain registration rights, customary for transactions of this kind.

With respect to Category 1 Programs, Wave will be responsible for researching and developing products and companion diagnostics for Category 1 Programs through completion of the first proof of mechanism study for such products. Takeda will have an exclusive option for each target and all associated products and companion diagnostics for such target, which it may exercise at any time through completion of the proof of mechanism study. If Takeda exercises this option, Wave will receive an opt-in payment and will lead manufacturing and joint clinical co-development activities and Takeda will lead joint co-commercial activities in the United States and all commercial activities outside of the United States. Global costs and potential profits will be shared 50:50 and Wave will be eligible to receive development and commercial milestone payments. In addition to its 50% profit share, Wave is eligible to receive option exercise fees and development and commercial milestone payments for each of the Category 1 Programs.

With respect to Category 2 Programs, Wave has granted Takeda the right to exclusively license multiple preclinical programs during a four-year research term (subject to limited extension for programs that were initiated prior to the expiration of the research term, in accordance with the Takeda Collaboration Agreement). During that term, the parties may collaborate on preclinical programs for up to six targets at any one time. Wave will be responsible for researching and preclinically developing products and companion diagnostics directed to the agreed upon targets through completion of IND-enabling studies in the first major market country. Thereafter, Takeda will have an exclusive worldwide license to develop and commercialize products and companion diagnostics directed to such targets, subject to Wave's retained rights to lead manufacturing activities for products directed to such targets. Takeda will fund Wave's research and preclinical activities in the amount of $60.0 million during the research term and will reimburse Wave for any collaboration-budgeted research and preclinical expenses incurred by Wave that exceed that amount. Wave is also eligible to receive tiered high single-digit to mid-teen royalties on Takeda's global commercial sales of products from each Category 2 Program.

Under the Takeda Collaboration Agreement, each party grants to the other party specific intellectual property licenses to enable the other party to perform its obligations and exercise its rights under the Takeda Collaboration Agreement, including license grants to enable each party to conduct research, development and commercialization activities pursuant to the terms of the Takeda Collaboration Agreement.

The term of the Takeda Collaboration Agreement commenced on April 2, 2018 and, unless terminated earlier, will continue until the date on which: (i) with respect to each Category 1 Program target for which Takeda does not exercise its option, the expiration or termination of the development program with respect to such target; (ii) with respect to each Category 1 Program target for which Takeda exercises its option, the date on which neither party is researching, developing or manufacturing any products or companion diagnostics directed to such target; or (iii) with respect to each Category 2 Program target, the date on which royalties are no longer payable with respect to products directed to such target.

Takeda may terminate the Takeda Collaboration Agreement for convenience on 180 days' notice, in its entirety or on a target-by-target basis. Subject to certain exceptions, each party has the right to terminate the Takeda Collaboration Agreement on a target-by-target basis if the other party, or a third party related to such party, challenges the patentability, enforceability or validity of any patents within the licensed technology that cover any product or companion diagnostic that is subject to the Takeda Collaboration Agreement. In the event of any material breach of the Takeda Collaboration Agreement by a party, subject to cure rights, the other party may terminate the Takeda Collaboration Agreement in its entirety if the breach relates to all targets or on a target-by-target basis if the breach relates to a specific target. In the event that Takeda and its affiliates cease development, manufacturing and commercialization activities with respect to compounds or products subject to the Takeda Collaboration Agreement and directed to a particular target, Wave may terminate the Takeda Collaboration Agreement with respect to such target. Either party may terminate the Takeda Collaboration Agreement for the other party's insolvency. In certain termination circumstances, Wave would receive a license from Takeda to continue researching, developing and manufacturing certain products, and companion diagnostics.

Asuragen

In November 2019, we entered into an agreement with Asuragen, Inc. ("Asuragen"), a molecular diagnostics company, for the development and potential commercialization of companion diagnostics for our investigational allele-selective therapeutic programs targeting HD. This collaboration aims to use Asuragen's market-leading repetitive sequence diagnostic expertise to provide scalable SNP phasing to support potential global development programs and future commercialization at a global level. Asuragen is leveraging its AmplideX® PCR technology to develop companion diagnostic tests designed to size and phase HTT CAG repeats with the three SNPs targeted by our WVE-120101, WVE-120102, and WVE-003 investigational therapeutic programs. These tests are designed to aid clinicians in selecting HD patients who could be appropriate for one or more of our HD compounds by identifying the SNPs that are in phase with the CAG-expanded allele.

Our Research Collaborations

University of Oxford; Professor Matthew Wood's Laboratory

Since April 2015, we have been collaborating with Dr. Matthew J.A. Wood, Professor of Neuroscience at the University of Oxford and Co-Director of the Oxford Centre for Neuromuscular Science under a translational research collaboration agreement with The Chancellor, Masters, and Scholars of the University of Oxford ("Oxford"). Dr. Wood's research is in the field of degenerative disorders of the nervous system and muscle. His laboratory's main focus is the investigation of novel therapeutic approaches using short nucleic acids to target mRNA. His team has been investigating the potential of single-stranded antisense oligonucleotides for the modification of mRNA splicing. In October 2016, we extended our research collaboration in order for Oxford to characterize our proprietary isomers in murine models to further improve the pharmacology of oligonucleotides using our novel chemistries.

University of Massachusetts Medical School

For our C9orf72 program, we have been working in collaboration with Dr. Robert H. Brown, Jr., the Leo P. and Theresa M. LaChance Chair in Medical Research and Chair of the Department of Neurology at UMMS, an internationally known researcher and physician in the field. Our work with UMMS is focused on characterizing our proprietary isomers in order to improve the pharmacology of oligonucleotides for the treatment of ALS and FTD, and investigating the mechanisms of action of specific and efficient knockdown of the targeted mutant C9orf72 mRNA.

Manufacturing

To provide internal cGMP manufacturing capabilities and increase control and visibility of our drug product supply chain, we entered into a lease in September 2016 for a multi-use facility of approximately 90,000 square feet in Lexington, Massachusetts and initiated the build out of manufacturing space and related capabilities. In addition to manufacturing space, the Lexington facility includes additional laboratory and office space. This facility supplements our existing Cambridge, Massachusetts laboratory and office space headquarters, enhances our ability to secure drug substance for current and future development activities and may provide commercial-scale manufacturing capabilities. In July 2017, we took occupancy of the Lexington facility and began manufacturing production in the fourth quarter of 2017.

We believe that we have sufficient manufacturing capacity through our third-party contract manufacturers and our internal manufacturing facility to meet our current research, clinical and early-stage commercial needs. We believe that the addition of our internal cGMP manufacturing capabilities, together with the supply capacity we have established externally, will be sufficient to meet our anticipated manufacturing needs for the next several years. We monitor the availability of capacity for the manufacture of drug substance and drug product and believe that our supply agreements with our contract manufacturers and the lead times for new supply agreements would allow us to access additional capacity if needed. We believe that our product candidates can be manufactured at scale and with production and procurement efficiencies that will result in commercially competitive costs.

Intellectual Property

We believe that we have a strong intellectual property position relating to the development and commercialization of our stereopure oligonucleotides. Our intellectual property portfolio includes filings designed to protect stereopure oligonucleotide compositions generally, as well as filings designed to protect stereopure compositions of oligonucleotides with particular stereochemical patterns (for example, that affect or confer biological activity). Our portfolio also includes filings for both proprietary methods and reagents, as well as various chemical methodologies that enable production of such stereopure oligonucleotide compositions. In addition, our portfolio includes filings designed to protect methods of using stereopure oligonucleotide compositions and filings designed to protect particular stereopure oligonucleotide products, such as those having a particular sequence, pattern of nucleoside and/or backbone modification, pattern of backbone linkages and/or pattern of backbone chiral centers.

We own or have rights to worldwide patent filings that protect our proprietary technologies for making stereopure oligonucleotide compositions, and that also protect the compositions themselves, as well as methods of using them, including in the treatment of diseases. Our portfolio includes multiple issued patents, including in major market jurisdictions such as the United States, Europe and Japan. We also have applications pending in multiple jurisdictions around the world, including these major market jurisdictions.

Synthetic Methodologies

Our patent portfolio includes multiple families that protect synthetic methodologies and/or reagents for generating stereopure oligonucleotide compositions. Certain synthetic methodologies and/or reagents are covered by families which include two issued Japanese patents that have terms that extend to 2022-2025.

Additional synthetic methodologies and/or reagents are protected by other families in our patent portfolio. Certain such families have 20-year expiration dates that range from 2029 to at least 2040. Some of these families have issued patents in several jurisdictions, including in major market jurisdictions such as the United States, Europe, and/or Japan, have pending applications in multiple jurisdictions including in these major market jurisdictions, or are in the international stage.

We also co-own with the University of Tokyo certain filings that are directed to certain methods and/or reagents for synthesizing oligonucleotides; their 20-year expiration dates fall in 2031.

Stereopure Oligonucleotide Compositions

Certain of our patent filings protect stereopure compositions, particularly of therapeutically relevant oligonucleotides. Some such filings are directed to compositions whose oligonucleotides are characterized by particular patterns of chemical modification (including modifications of bases, sugars and/or internucleotidic linkages) and/or of internucleotidic linkage stereochemistry. Certain patent filings describe specific compositions designed for use in the treatment of particular diseases. Several of our patent filings directed to stereopure compositions have entered national stage prosecution in multiple jurisdictions and some have issued in one or more jurisdictions; others are in the international stage. Certain filings offer 20-year protection terms that range from 2033 to at least 2040.

We also co-own with Shin Nippon Biomedical Laboratories, Ltd. various patent families, some of which include one or more issued patents, including in major market jurisdictions; these filings have 20-year terms extending to 2033-2035.

Future Filings

We maintain a thoughtful and ambitious program for developing and protecting additional intellectual property, including new synthetic methodologies and reagents. We also intend to prepare and submit patent filings specifically directed to protecting individual product candidates and their uses as we finalize leads and collect relevant data, which is expected to include comparison data confirming novel and/or beneficial attributes of our product candidates.

Singapore Intellectual Property Law

Section 34 of the Singapore Patents Act provides that a person residing in Singapore is required to obtain written authorization from the Singapore Registrar of Patents (the "Registrar") before filing an application for a patent for an invention outside of Singapore, unless all of the following conditions have been satisfied: (a) the person has filed an application for a patent for the same invention in the Singapore Registry of Patents at least two months before the filing of the patent application outside Singapore, and (b) the Singapore Registrar of Patents has not, in respect of this patent application, given directions to prohibit or restrict the publication of information contained in the patent application or its communication to any persons or description of persons pursuant to Section 33 of the Singapore Patents Act, or if the Registrar has given any such directions, all such directions have been revoked. A violation of Section 34 is a criminal offense punishable by a fine not exceeding S$5,000, or imprisonment for a term not exceeding two years, or both. There have been some instances where we have undertaken filings outside of Singapore, and there may be instances where we are required to make such filings in the future, without first obtaining written authorization from the Registrar. We have notified the Registrar of such filings and we have since implemented measures to address the requirements of Section 34 moving forward. To date, the Registrar has offered a compound of some of the offences considered against payment of a sum of S$50 to S$100 per considered case. Under Singapore law, the Registrar has discretion to offer a compound of such offences against payment of a sum of money of up to S$2,000, or to prosecute the offence subject to the other penalties noted above. There remain approximately 40 patent applications in multiple patent families which we have notified the Intellectual Property Office of Singapore ("IPOS") of where Section 34 requirements have not been complied with, and are pending IPOS' decision thereon. We cannot assure you that the Registrar will offer to compound any such violations of Section 34, or that any offer to compound will be for an amount similar to previous compound offers.

Competition

The biotechnology and pharmaceutical marketplace is characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our expertise in oligonucleotides, scientific knowledge and intellectual property estate provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions, governmental agencies and public and private research institutions. Not only must we compete with other companies that are focused on oligonucleotides, but any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

Many of our competitors may 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. 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. Mergers and acquisitions in the pharmaceutical, biotechnology and diagnostic 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.

Huntington's Disease

T There are no approved treatments available to slow the progression of HD. We believe, based on publicly available information, that Annexon Biosciences (Phase 2), Ionis Pharmaceuticals and Roche (Phase 3), Mitochon Pharmaceuticals (Phase 1), Novartis (Phase 1 completed), Prilenia Therapeutics (Phase 3), PTC Therapeutics (Phase 1), uniQure (Phase 1), and Vaccinex (Phase 2 completed) all have investigational drugs in clinical development.

Several companies have ongoing preclinical programs for HD, including Alnylam Pharmaceuticals, AskBio, Atalanta Therapeutics, and Biogen, Avergen Pharmaceuticals, Mitoconix Bio, NeuBase Therapeutics, Neurimmune, Novartis, Nuredis, PTC Therapeutics, Sangamo Therapeutics and Takeda, Spark Therapeutics, Triplet Therapeutics, Vertex Pharmaceuticals, and Voyager Therapeutics.

A number of companies are developing molecules to treat symptoms associated with HD, including Azevan Pharmaceuticals (Phase 2), Alterity Therapeutics (Phase 2), Sage Therapeutics (Phase 1), and Stealth BioTherapeutics (Phase 2), among others.

Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

There are two treatments approved in the United States for the treatment of ALS: riluzole, approved in 1995, and edaravone, approved in 2017. There are a number of companies with potential therapeutics for the treatment of ALS in clinical development, including Amylyx Pharmaceuticals (Phase 2/3), AB Sciences (Phase 3 completed), Orphazyme (Phase 3), BrainStorm Cell Therapeutics (Phase 3 completed), (Phase 1 completed), Biogen (Phase 1), Biohaven Pharmaceuticals (Phase 2/3), and ALS TDI (Phase 1 completed). We believe that only one company, Biogen (Phase 1), has initiated a clinical trial targeting ALS due to a C9orf72 mutation in the United States.

Several companies have ongoing preclinical programs for ALS that may directly or indirectly target patients with the C9orf72 mutation including AcuraStem, AGTC, Biogen and Neurimmune, Locana Bio, MeiraGTx, Passage Bio, Pfizer and Sangamo Therapeutics, and uniQure.

There are no approved treatments available to slow the progression of FTD. Few companies have investigational therapies in clinical development specifically for FTD. Ionis Pharmaceuticals /Biogen (Phase 1) and AlzProTect (Phase 1) appear to be including FTD in their broader AD or tauopathies clinical development plans. Alector (Phase 2) is including FTD patients with a C9orf72 mutation in a larger clinical program.

There are several companies though with ongoing preclinical programs for FTD that may directly or indirectly target patients with the C9orf72 mutation including AGTC, Denali Therapeutics and Takeda, Locano Bio, Passage Bio, Pfizer and Sangamo Therapeutics, and uniQure.

Duchenne Muscular Dystrophy

Sarepta Therapeutics' Vyondys 53 (golodirsen), an exon skipping nucleic acid therapeutic, was approved by the FDA for the treatment of DMD in the United States in 2019. The FDA concluded that the data submitted demonstrated an increase in dystrophin production that is reasonably likely to predict clinical benefit in some patients with DMD who have a confirmed mutation of the DMD gene amenable to exon 53 skipping. No clinical benefit of golodirsen has been established. Thus, in accordance with the U.S. accelerated approval regulations, the FDA is requiring Sarepta to conduct a clinical trial to verify and describe the drug's clinical benefit. The required study would need to assess whether golodirsen improves motor function of DMD patients with a confirmed mutation of the DMD gene amenable to exon 53 skipping. If the trial fails to verify clinical benefit, the FDA could initiate proceedings to withdraw approval of the drug.

NS Pharma's Viltepso (viltolarsen), an exon skipping nucleic acid therapeutic, was approved by the FDA for the treatment of DMD in the United States in 2020. The FDA concluded that the data submitted demonstrated an increase in dystrophin production that is reasonably likely to predict clinical benefit in some patients with DMD who have a confirmed mutation of the DMD gene amenable to exon 53 skipping. NS Pharma has been required by the FDA to conduct a clinical trial to confirm the drug's clinical benefit. The study is designed to assess whether viltolarsen improves the time to stand for DMD patients amenable to exon 53 skipping. If the trial fails to verify clinical benefit, the FDA may initiate proceedings to withdraw approval of the drug.

Several other companies have investigational drugs in clinical development directly targeting patients amenable to exon 53 skipping or DMD more broadly. These include Astellas Pharma (Phase 1), FibroGen (Phase 3), Pfizer (Phase 3), PTC Therapeutics (Phase 2), Santhera Pharmacauticals (Phase 3), Sarepta Therapeutics (Phase 2), and Solid Biosciences (Phase 2).

Several companies also have ongoing preclinical programs for DMD that may directly or indirectly target patients amenable to exon 53 skipping. These companies include Audentes Therapeutics, Catabasis Pharmaceuticals, CRISPR Therapeutics, Dystrogen Therapeutics, FibroGen, Fulcrum Therapeutics, Immunoforge, PepGen, Precision BioSciences, Sarepta Therapeutics, and Strykagen. among others.

Alpha-1 Antitrypsin Deficiency ("AATD")

There are five treatments approved in the US for AATD: Prolastin, Prolastin-C, Aralast NP, Zemaira, and Glassia. All five contain plasma-derived human alpha1-proteinase inhibitor and are indicated for chronic augmentation and maintenance therapy in adults with emphysema due to congenital deficiency of alpha1-proteinase inhibitor (Alpha1-PI). The FDA also notes in the prescribing information for each that the effect of augmentation therapy with any alpha1-proteinase inhibitor on pulmonary exacerbations and on the progression of emphysema in Alpha1-PI deficiency has not been demonstrated in randomized, controlled clinical trials.

There are also a number of companies with investigational drugs in clinical development: Arrowhead Pharmaceuticals and Takeda (Phase 3), Vertex (Phase 2), Dicerna Pharmaceuticals and Alnylam Pharmaceuticals (Phase 2), Mereo BioPharma (Phase 2), InhibRx (Phase 2), AGTC (Phase 2) and Santhera Pharmacauticals (Phase 1 completed).

There are also several companies with ongoing preclinical programs for AATD including Apic Bio, Beam Therapeutics, Editas Medicine, Intellia Therapeutics, LogicBio Therapeutics, Sangamo Therapeutics, Shape Therapeutics, and Vertex , among others.

ADAR-mediated RNA Editing ("ADAR-editing")

The are several companies pursuing editing approaches that may compete with our ADAR-editing modality. These include companies developing investigational drugs via viral and non-viral delivery for RNA editing (Shape Therapeutics and Korro Bio), DNA base-editing (Beam), and DNA editing (Editas Medicine, Intellia Therapeutics, and Sangamo Therapeutics), among others. These companies may leverage these approaches to target the same indications that we intend to target or indications where we do not currently plan to compete.

Government Regulation

FDA Approval Process for Drug Products

In the United States, pharmaceutical products are subject to extensive regulation by the FDA. The Federal Food, Drug and Cosmetic Act ("FDCA"), and other federal and state statutes and regulations, govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling, and import and export of pharmaceutical products. Failure to comply with applicable FDA or other requirements may subject a pharmaceutical company to a variety of administrative or judicial sanctions, such as the FDA's refusal to approve pending applications, a clinical hold, warning letters, recall or seizure of drug products, partial or total suspension of production, withdrawal of drug products from the market, injunctions, fines, civil penalties or criminal prosecution.

FDA approval is required before any new drug, such as a new molecular or chemical entity, or a new dosage form, new use or new route of administration of a previously approved product, can be marketed in the United States. The process required by the FDA before a new drug product may be marketed in the United States generally involves:

- completion of preclinical laboratory and animal testing in compliance with applicable FDA good laboratory practice regulations and other requirements ("GLP");
- submission to the FDA of an Investigational New Drug application ("IND") for human clinical testing which must become effective before human clinical trials may begin in the United States;
- approval by an independent institutional review board ("IRB") at each site where a clinical trial will be performed before the trial may be initiated at that site;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practice ("GCP") to establish safety and substantial evidence of effectiveness of the proposed product candidate for each intended use;
- thorough characterization of the product candidate and establishment of acceptable standards to assure its purity, identity, strength, quality and stability in compliance with current cGMP;

- satisfactory completion of an FDA pre-approval inspection of the facility or facilities at which the product is manufactured to assess compliance with cGMP;
- satisfactory completion of an FDA pre-approval inspection of one or more clinical trial site(s) or the sponsor's site and/or contract research organization responsible for conduct of key clinical trials in accordance with GCP;
- submission to the FDA of a New Drug Application ("NDA"), which must be accepted for filing by the FDA;
- completion of an FDA advisory committee review, if applicable;
- payment of user fees, if applicable; and
- FDA review and approval of the NDA.

The manufacturing development, preclinical and clinical testing, and review process requires substantial time, effort and financial resources. Manufacturing development includes laboratory evaluation of product chemistry, formulation, development of manufacturing and control procedures, evaluation of stability, and the establishment of procedures to ensure continued product quality.

Nonclinical tests include *in vitro* and in vivo animal studies to assess the toxicity and other safety characteristics of the product candidate, as well as other important aspects of drug pharmacology. The results of nonclinical tests, together with manufacturing information, analytical data and a proposed clinical trial protocol and other information, are submitted as part of an IND to the FDA. Some long-term nonclinical testing to further establish the safety profile of the product candidate, as well as manufacturing processes development and drug quality evaluation, continues after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises concerns or questions related to the proposed clinical trial and places the IND on a clinical hold. In such a case, the IND sponsor must resolve all outstanding concerns before the clinical trial can begin. As a result, our submission of an IND may not result in FDA authorization to commence a clinical trial. A separate submission to an existing IND must also be made for each successive clinical trial conducted during product development, or if changes are made in trial design. Even if the IND becomes effective and the trial proceeds without initial FDA objection, the FDA may stop the trial at a later time if it has concerns, such as if unacceptable safety risks arise.

Further, an independent IRB at each site proposing to conduct the clinical trial must review and approve the plan for any clinical trial and informed consent information for subjects before the trial commences at that site and it must perform an ongoing review of the research on an annual basis until the trial is completed. The FDA or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk or that the trials are not being conducted in accordance with the clinical plan or in compliance with GCP. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients.

Clinical trials involve the administration of the product candidate to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Sponsors of clinical trials generally must register and report, at the National Institutes of Health ("NIH")-maintained website clinicaltrials.gov, key parameters of a clinical trial. For purposes of an NDA submission, human clinical trials are typically conducted in the following sequential phases, which may overlap or be combined:

- ***Phase 1.*** The product is initially introduced into healthy human subjects or patients and tested for safety, dose tolerance, absorption, metabolism, distribution and excretion and, if possible, to gain an early indication of its effectiveness.
- ***Phase 2.*** The product is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted indications and to determine dose tolerance and optimal dosage. Multiple Phase 2 clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more extensive clinical trials.
- ***Phase 3.*** These are commonly referred to as pivotal studies. When Phase 2 evaluations demonstrate that a dose range of the product appears to be effective and has an acceptable safety profile, trials are undertaken in larger patient populations to further evaluate dosage, to obtain substantial, statistical evidence of clinical efficacy and safety, generally at multiple, geographically-dispersed clinical trial sites, to establish the overall risk-benefit relationship of the product and to provide adequate information for approval of the product.
- ***Phase 4.*** In some cases, the FDA may condition approval of an NDA for a product candidate on the sponsor's agreement to conduct additional clinical trials to further assess the product's safety and effectiveness after NDA approval. Such post-approval trials are typically referred to as Phase 4 studies.

Progress reports detailing progress and safety data gathered from clinical trials must be submitted at least annually to the FDA. Safety reports are submitted more frequently if certain serious adverse effects, or SAEs, occur. Phase 1, Phase 2 and Phase 3 clinical trials

may not be completed successfully within any specified period, or at all. The FDA will typically inspect one or more clinical sites to assure compliance with GCP and the integrity of the clinical data submitted as part of NDA review. Information related to the product, patient population, phase of investigation, study sites and investigators and other aspects of the clinical trial is made public as part of the registration of the clinical trial. Sponsors are also obligated to disclose the results of most clinical trials after completion, although in some cases disclosure of the results of these trials can be delayed for up to two years after the trial completion date. Competitors may use this publicly available information to gain knowledge regarding the progress of development programs.

Assuming successful completion of the required clinical testing, the results of the preclinical studies and clinical trials, along with information relating to the product's pharmacology, chemistry, manufacturing, and controls, and proposed labeling, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. Data may come from company-sponsored clinical trials intended to test the safety and efficacy of a product's use or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and efficacy of the investigational product to the satisfaction of the FDA. Under federal law, the fee for the submission of an NDA with clinical data is substantial (for example, for FY2021 this application fee exceeds $2.8 million), and the sponsor of an approved NDA is also subject to an annual program fee, currently more than $330,000 per program. These fees are typically adjusted annually, but exemptions and waivers may be available under certain circumstances, including NDA fees for products with orphan designation.

The FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. Any resubmitted application, following a refusal to file action, is also subject to 60-day review before the FDA accepts it for filing.

Under the PDUFA, for original NDAs, the FDA has ten months from the filing date in which to complete its initial review of a standard application and respond to the applicant, and six months from the filing date for an application with priority review. For all new molecular entity, or NME, NDAs, the ten and six-month time periods run from the filing date; for all other original applications, the ten and six-month time periods run from the submission date. Despite these review goals, it is not uncommon for FDA review of an NDA to extend beyond the goal date.

Once the submission has been accepted for filing, the FDA begins an in-depth review. As noted above, the FDA has agreed to specified performance goals in the review process of NDAs. Most such applications are meant to be reviewed within ten months from the date it is accepted for filing (i.e., 12 months), and most applications for "priority review" products are meant to be reviewed within six months from the date the application is accepted for filing (i.e., 8 months). The review process may be extended by the FDA for three additional months to consider new information or in the case of a clarification provided by the applicant to address an outstanding deficiency identified by the FDA following the original submission.

Before approving an NDA, the FDA may inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP. The FDA may also inspect one or more of the clinical sites where pivotal trials were conducted and the contract research organization facilities with oversight of the trial, in order to ensure compliance with GCP and the integrity of the study data.

Additionally, the FDA may refer any NDA, including applications for novel biologic candidates which present difficult questions of safety or efficacy, to an advisory committee. Typically, an advisory committee is a panel of independent experts, including clinicians and other scientific experts that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendation of an advisory committee, but it considers such recommendations when making final decisions on approval. The FDA likely will re-analyze the clinical trial data, which could result in extensive discussions between the FDA and the applicant during the review process. The FDA also may require submission of a risk evaluation and mitigation strategy, or REMS, if it determines that a REMS is necessary to ensure that the benefits of the drug outweigh its risks and to assure the safe use of the drug or biological product. The REMS could include medication guides, physician communication plans, assessment plans and/or elements to assure safe use, such as restricted distribution methods, patient registries or other risk minimization tools. The FDA determines the requirement for a REMS, as well as the specific REMS provisions, on a case-by-case basis. If the FDA concludes a REMS is needed, the sponsor of the NDA must submit a proposed REMS. The FDA will not approve an NDA without a REMS, if required.

Under the Pediatric Research Equity Act, or PREA, as amended, an NDA or supplement to an NDA must contain data that are adequate to assess the safety and efficacy of the product candidate for the claimed indications in all relevant pediatric populations and to support dosing and administration for each pediatric population for which the product is safe and effective. The FDA may grant deferrals for submission of pediatric data or full or partial waivers. The Food and Drug Administration Safety and Innovation Act, or the FDASIA, enacted in 2012, made permanent PREA to require a sponsor who is planning to submit a marketing application for a product that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration to submit an initial Pediatric Study Plan, or PSP, within sixty days of an end-of-Phase 2 meeting or, if there is no such meeting, as early

as practicable before the initiation of the Phase 3 or Phase 2/3 clinical trial. The initial PSP must include an outline of the pediatric study or studies that the sponsor plans to conduct, including trial objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. The FDA and the sponsor must reach an agreement on the PSP. A sponsor can submit amendments to an agreed upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from pre-clinical studies, early phase clinical trials or other clinical development programs.

The FDA reviews an NDA to determine, among other things, whether a product is safe and effective for its intended use and whether its manufacturing is cGMP-compliant to assure and preserve the product's identity, strength, quality and purity. The approval process is lengthy and often difficult, and the FDA may refuse to approve an NDA if the applicable regulatory criteria are not satisfied or may require additional clinical or other data and information. On the basis of the FDA's evaluation of the NDA and accompanying information, including the results of the inspection of the manufacturing facilities, it may issue an approval letter or a Complete Response Letter (CRL). An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A CRL indicates that the review cycle for an application is complete and that the application will not be approved in its present form. CRLs outline the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. The CRL may require additional clinical or other data, additional pivotal Phase 3 clinical trial(s) and/or other significant and time-consuming requirements related to clinical trials, preclinical studies or manufacturing. If a CRL is issued, the applicant may choose to either resubmit the NDA or NDA addressing all of the deficiencies identified in the letter, or withdraw the application. The FDA has committed to reviewing such resubmissions in response to an issued CRL in either two or six months depending on the type of information included. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when the deficiencies have been addressed to the FDA's satisfaction, the FDA will typically issue an approval letter.

The FDA may withdraw product approval if ongoing regulatory requirements are not met or if safety problems are identified after the product reaches the market. In addition, the FDA may require post-approval testing, including Phase 4 studies, and surveillance programs to monitor the effect of approved products which have been commercialized, and the FDA has the authority to prevent or limit further marketing of a product based on the results of these post-marketing programs. Products may be marketed only for the approved indications and in accordance with the provisions of the approved label and, even if the FDA approves a product, the FDA may limit the approved indications for use for the product or impose other conditions, including labeling or distribution restrictions or other risk-management mechanisms, such as a Boxed Warning, which highlights a serious safety concern that should be mitigated under a REMS program. Further, if there are any modifications to the product, including changes in indications, labeling, or manufacturing processes or facilities, a company is generally required to submit and obtain FDA approval of a supplemental NDA, which may require the company to develop additional data or conduct additional nonclinical studies and clinical trials.

Fast Track, Breakthrough Therapy and Priority Review Designations

The FDA is authorized to designate certain products for expedited development or review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs include fast track designation, breakthrough therapy designation and priority review designation.

To be eligible for a fast track designation, the FDA must determine, based on the request of a sponsor, that a product is intended to treat a serious or life-threatening disease or condition and demonstrates the potential to address an unmet medical need by providing a therapy where none exists or a therapy that may be potentially superior to existing therapy based on efficacy or safety factors. Fast track designation provides opportunities for more frequent interactions with the FDA review team to expedite development and review of the product. The FDA may also review sections of the NDA for a fast track product on a rolling basis before the complete application is submitted, if the sponsor and the FDA agree on a schedule for the submission of the application sections and the sponsor pays any required user fees upon submission of the first section of the NDA. In addition, fast track designation may be withdrawn by the sponsor or rescinded by the FDA if the designation is no longer supported by data emerging from the clinical trial process.

In addition, with the enactment of FDASIA in 2012, Congress created a new regulatory program for product candidates designated by FDA as "breakthrough therapies" upon a request made by the IND sponsors. A breakthrough therapy is defined as a drug or biologic that is intended, alone or in combination with one or more other drugs or biologics, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug or biologic may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Drugs or biologics designated as breakthrough therapies are also eligible for accelerated approval of their respective marketing applications. The FDA must take certain actions with respect to breakthrough therapies, such as holding timely meetings with and providing advice to the product sponsor, which are intended to expedite the development and review of an application for approval of a breakthrough therapy.

Finally, the FDA may designate a product for priority review if it is a drug or biologic that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness over existing therapy. The FDA determines at the time that the marketing application is submitted, on a case- by-case basis, whether the proposed drug represents a significant improvement in treatment, prevention or diagnosis of disease when compared with other available therapies. Significant improvement may be illustrated by evidence of increased effectiveness in the treatment of a condition, elimination or substantial reduction of a treatment-limiting drug reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, or evidence of safety and effectiveness in a new subpopulation. A priority review designation is intended to direct overall attention and resources to the evaluation of such applications, and to shorten the FDA's goal for taking action on a marketing application from ten months to six months for an NME NDA from the date of filing.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened. Furthermore, fast track designation, breakthrough therapy designation and priority review do not change the standards for approval and may not ultimately expedite the development or approval process.

Accelerated Approval Pathway

In addition, products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval from the FDA and may be approved on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. The FDA may also grant accelerated approval for such a drug or biologic when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, or IMM, and that is reasonably likely to predict an effect on IMM or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA will require that a sponsor of a drug receiving accelerated approval perform post-marketing clinical trials to verify and describe the predicted effect on IMM or other clinical endpoint, and the product may be subject to expedited withdrawal procedures. Drugs and biologics granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. Surrogate endpoints can often be measured more easily or more rapidly than clinical endpoints. An intermediate clinical endpoint is a measurement of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on IMM. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints, but has indicated that such endpoints generally may support accelerated approval when the therapeutic effect measured by the endpoint is not itself a clinical benefit and basis for traditional approval, if there is a basis for concluding that the therapeutic effect is reasonably likely to predict the ultimate long-term clinical benefit of a drug.

The accelerated approval pathway is most often used in settings in which the course of a disease is long and an extended period of time is required to measure the intended clinical benefit of a drug, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. For example, accelerated approval has been used extensively in the development and approval of drugs for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large clinical trials to demonstrate a clinical or survival benefit.

The accelerated approval pathway is usually contingent on a sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the drug's clinical benefit. As a result, a product candidate approved on this basis is subject to rigorous post-marketing compliance requirements, including the completion of Phase 4 or post-approval clinical trials to confirm the effect on the clinical endpoint. Failure to conduct required post-approval studies, or to confirm the predicted clinical benefit of the product during post-marketing studies, would allow the FDA to withdraw approval of the drug. All promotional materials for product candidates being considered and approved under the accelerated approval program are subject to prior review by the FDA.

Modernizing Trial Design

FDA sometimes initiates pilot programs to facilitate communication or other aspects of development to help advance approval of new drugs. In August 2018, the FDA announced the establishment of a Complex Innovative Trial Design ("CID") Pilot Meeting Program ("CID pilot program") to facilitate the use of CID approaches in late-stage drug development and promote innovation by allowing the FDA to publicly discuss the trial designs considered through the pilot program, including for medical products that have not yet been approved by the FDA. Under the CID pilot program, the FDA will accept up to two applicants per quarter. For each meeting request granted as part of the pilot, the FDA will conduct an initial meeting and a follow-up meeting on the same CID and medical product

within a span of approximately 120 days. Our Phase 2/3 clinical trial of suvodirsen for DMD, which in December 2019 we announced our decision to discontinue, was the first trial selected for the CID pilot program.

Post-Approval Requirements

Once an NDA is approved, a product will be subject to continuing regulation by the FDA, including, among other things, requirements relating to safety surveillance and adverse event reporting, periodic reporting, continued cGMP compliance and quality oversight, compliance with post-marketing commitments, recordkeeping, advertising and promotion, and reporting manufacturing and labeling changes, as applicable.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs (including third-party manufacturers) are required to register their establishments with the FDA and some state agencies and are subject to periodic unannounced inspections by the FDA and some state agencies for assessment of compliance with cGMP. Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction, and sometimes notification of, any deviations from cGMP. These regulations impose reporting and documentation requirements on the sponsor and any third-party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Discovery of previously unknown problems with a product, including adverse events of unlisted severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements such as noncompliance with cGMP or failure to correct previously identified inspection findings, may result in mandatory revisions to the approved labeling to add new safety information; imposition of post-market or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- issuance of field alerts, restrictions on the marketing or manufacturing of the product, product recalls, or complete withdrawal of the product from the market;
- fines, warning letters or other enforcement-related letters or holds on clinical trials using the product or other products manufactured at the same facility;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product approvals;
- product seizure or detention, or refusal to permit the import or export of products;
- injunctions, consent decrees, or the imposition of civil or criminal penalties; And
- consent decrees, corporate integrity agreements, debarment, or exclusion from federal health care programs; or mandated modification of promotional materials and labeling and the issuance of corrective information.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. While physicians may generally prescribe a drug for off-label uses, manufacturers may only promote the drug in accordance with the data provided in the approved product label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have promoted false and misleading information about the product may be subject to significant liability, both at the federal and state levels.

The FDA has authority to require a REMS from manufacturers to ensure that the benefits of a drug or biological product outweigh its risks. In determining whether a REMS is necessary, the FDA may consider the size of the population likely to use the drug, the seriousness of the disease or condition to be treated, the expected benefit of the drug, the duration of treatment, the seriousness of known or potential adverse events, and whether the drug is an NME. If the FDA determines a REMS is necessary, the drug sponsor must agree to the REMS plan at the time of approval, or at a later date should significant new risk information come to light. A REMS may be required to include various elements, such as a medication guide, a communication plan to educate healthcare providers of the drug's risks, limitations on who may prescribe or dispense the drug, or other elements to assure safe use that the FDA deems necessary to assure the benefits of use of the drug outweigh its risks. In addition, the REMS must include a timetable to assess the strategy, often at 18 months, 3 years, and 7 years after the strategy's approval. The FDA may also impose a REMS requirement on a drug already on the market if the FDA determines, based on new safety information, that a REMS is necessary to ensure that the drug's benefits outweigh its risks.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription drug product samples

and impose requirements to ensure accountability in distribution. Most recently, the Drug Supply Chain Security Act, or DSCSA, was enacted with the aim of building an electronic system to identify and trace certain prescription drugs distributed in the United States. The DSCSA mandates phased-in and resource-intensive obligations for pharmaceutical manufacturers, wholesale distributors, and dispensers over a 10-year period that is expected to culminate in November 2023. From time to time, new legislation and regulations may be implemented that could significantly change the statutory provisions governing the approval, manufacturing and marketing of products regulated by the FDA. It is impossible to predict whether further legislative or regulatory changes will be enacted, or FDA regulations, guidance or interpretations changed or what the impact of such changes, if any, may be.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug intended to treat a rare disease or condition, which is defined as one affecting fewer than 200,000 individuals in the United States or more than 200,000 individuals where there is no reasonable expectation that the product development cost will be recovered from product sales in the United States. Orphan drug designation must be requested before submitting an NDA. After the FDA grants orphan drug designation, the identity of the drug and its potential orphan use will be disclosed publicly by the FDA; the posting will also indicate whether a drug is no longer designated as an orphan drug. More than one product candidate may receive an orphan drug designation for the same indication. Orphan drug designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

Under PREA, submission of a pediatric assessment is not required for pediatric investigation of a product that has been granted orphan drug designation. However, under the FDA Reauthorization Act of 2017 (“FDASIA”) the scope of the PREA was extended to require pediatric studies for products intended for the treatment of an adult cancer that are directed at a molecular target that are determined to be substantially relevant to the growth or progression of a pediatric cancer. In addition, the FDA finalized guidance in 2018 indicating that it does not expect to grant any additional orphan drug designation to products for pediatric subpopulations of common diseases. Nevertheless, FDA intends to still grant orphan drug designation to a drug or biologic that otherwise meets all other criteria for designation when it prevents, diagnoses or treats either (i) a rare disease that includes a rare pediatric subpopulation, (ii) a pediatric subpopulation that constitutes a valid orphan subset, or (iii) a rare disease that is in fact a different disease in the pediatric population as compared to the adult population.

If an orphan drug-designated product subsequently receives FDA approval for the disease for which it was designed, the product will be entitled to seven years of product exclusivity, which means that the FDA may not approve any other applications to market the same drug for the same indication, except in very limited circumstances, for seven years. Orphan exclusivity does not block the approval of a different drug or biologic for the same rare disease or condition, nor does it block the approval of the same drug or biologic for different conditions. If a competitor obtains approval of the same drug, as defined by the FDA, or if our product candidate is determined to be the same drug as a competitor’s product for the same indication or disease, the competitor’s exclusivity could block the approval of our product candidate in the designated orphan indication for seven years, unless our product is demonstrated to be clinically superior to the competitor’s drug.

European Union Orphan Drug Designation

In the European Union (the “EU”), orphan drug designation by the European Commission (the “EC”) provides regulatory and financial incentives for companies to develop and market therapies that meet the following requirements: (1) the product is intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions; (2) either (a) such condition affects no more than five in 10,000 persons in the European Union when the application is made, or (b) the product, without the benefits derived from orphan status, would not generate sufficient return in the European Union to justify investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the European Union, or if such a method exists, the product will be of significant benefit to those affected by the condition, as defined in Regulation (EC) 847/2000. To be considered for orphan drug designation in the EU, companies must provide data that demonstrate the plausibility for use of the investigational therapy in the treatment of the disease and establish that the drug has the potential to provide relevant advantages or a major contribution to patient care over existing therapies.

Among the incentives available to medicines designated as orphan drugs by the EC are ten-year market exclusivity in the EU after product approval, eligibility for conditional marketing authorization, protocol assistance from the European Medicines Agency at reduced fees during the product development phase and direct access to centralized marketing authorization in the EU. The exclusivity period may be reduced to six years if, at the end of the fifth year, the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. In addition, marketing authorization may be granted to a similar medicinal product with the same orphan indication during the ten-year period with the consent of the marketing authorization holder for the original orphan medicinal product or if the manufacturer of the original orphan medicinal product is unable to supply sufficient quantities of the product. Marketing authorization may also be granted to a similar medicinal product with the same orphan indication if the similar product is deemed safer, more effective or otherwise clinically superior to the original orphan medicinal product. Orphan drug designation must be requested before submitting an application for marketing authorization. Orphan drug designation does not, in itself, convey any advantage in, or shorten the duration of, the regulatory review and authorization process.

Pediatric Exclusivity and Pediatric Use

The Best Pharmaceuticals for Children Act ("BPCA") provides NDA holders a six-month period of non-patent marketing exclusivity attached to any other exclusivity listed with FDA—patent or non-patent—for a drug if certain conditions are met. Conditions for pediatric exclusivity include a determination by the FDA that information relating to the use of a new drug in the pediatric population may produce health benefits in that population; a written request by the FDA for pediatric studies; and agreement by the applicant to perform the requested studies and the submission to the FDA, completion of the studies in accordance with the written request, and the acceptance by the FDA, of the reports of the requested studies within the statutory timeframe. The data do not need to show the product to be effective in the pediatric population studied; rather, if the clinical trial is deemed to fairly respond to the FDA's request, the additional protection is granted. If reports of requested pediatric studies are submitted to and accepted by the FDA within the statutory time limits, whatever statutory or regulatory periods of exclusivity or patent protection cover the product are extended by six months. This is not a patent term extension, but it effectively extends the regulatory period during which the FDA cannot approve another application. The issuance of a written request does not require the sponsor to undertake the described studies. Applications under the BPCA are treated as priority applications.

The Hatch-Waxman Act and Marketing Exclusivity

In 1984, with passage of the Hatch-Waxman Amendments to the FDC Act, Congress authorized the FDA to approve generic drugs that are the same as drugs previously approved by the FDA under the NDA provisions of the statute and also enacted Section 505(b)(2) of the FDC Act. To obtain approval of a generic drug, an applicant must submit an abbreviated new drug application, or ANDA, to the agency. In support of such applications, a generic manufacturer may rely on the preclinical and clinical testing conducted for a drug product previously approved under an NDA, known as the reference listed drug, or RLD. Specifically, in order for an ANDA to be approved, the FDA must find that the generic version is identical to the RLD with respect to the active ingredients, the route of administration, the dosage form, and the strength of the drug. At the same time, the FDA must also determine that the generic drug is "bioequivalent" to the innovator drug.

Upon NDA approval of a new chemical entity or NCE, which is a drug that contains no active moiety that has been approved by the FDA in any other NDA, that drug receives five years of marketing exclusivity. During the exclusivity period, the FDA cannot accept for review any ANDA or 505(b)(2) NDA submitted by another company for another version of such drug where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted one year before NCE exclusivity expires if a Paragraph IV certification is filed on an NCE patent and any time after approval if the application is filed based on a new indication or a new formulation.

The Hatch-Waxman Act also provides three years of data exclusivity for a NDA, 505(b)(2) NDA or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example, new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the conditions of use associated with the new clinical investigations and does not prohibit the FDA from approving follow-on applications for drugs containing the original active agent. If there is no listed patent in the Orange Book, there may not be a Paragraph IV certification, and, thus, no ANDA or 505(b)(2) NDA may be filed before the expiration of the exclusivity period. Five-year and three-year exclusivity also will not delay the submission or approval of a traditional NDA filed under Section 505(b)(1) of the FDC Act. However, an applicant submitting a traditional NDA would be required to either conduct or obtain a right of reference to all of the preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Patent Term Restoration

Depending upon the timing, duration and specifics of FDA approval of the use of our therapeutic candidates, some of our U.S. patents may be eligible for limited patent term extension under the Hatch-Waxman Act. The Hatch-Waxman Act permits a patent restoration term of up to five years as compensation for any patent term lost during product development and the FDA regulatory review process.

However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of an NDA, plus the time between the submission date of an NDA and the approval of that application. Only one patent applicable to an approved drug is eligible for the extension and the application for extension must be made prior to the expiration of the patent. The United States Patent and Trademark Office, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we intend to apply for restorations of patent term for some of our currently owned or licensed patents to add patent life beyond their current expiration date, depending on the expected length of clinical trials and other factors involved in the submission of the relevant NDA.

In Vitro Diagnostic Tests for Biomarkers

For some of our product candidates, we plan to work with collaborators to develop or obtain access to *in vitro* companion diagnostic tests to identify appropriate patients for these targeted therapies. If a sponsor or the FDA believes that a diagnostic test is essential for the safe and effective use of a corresponding therapeutic product, a sponsor will typically work with a collaborator to develop an *in vitro* diagnostic ("IVD"). IVDs are regulated by the FDA as medical devices, and since 2014 the agency has issued final and draft guidance documents that are intended to assist companies developing *in vitro* companion diagnostic devices and companies developing therapeutic products that depend on the use of a specific *in vitro* companion diagnostic for the safe and effective use of the product.

The three types of marketing pathways for medical devices are clearance of a premarket notification under Section 510(k) of the Federal Food, Drug, and Cosmetic Act, or 510(k), approval of a premarket approval application, or PMA, and a *de novo* classification request, or *de novo*. If a company is required to perform clinical trials to support the safety and effectiveness of an IVD, and the IVD is viewed as a significant risk device, the sponsor will have to submit an investigational device exemption application, or IDE, to the FDA, which is similar in format and function to an IND. If the diagnostic test and the therapeutic drug are studied together to support their respective approvals, any clinical trials involving both product candidates must meet both the IDE and IND requirements.

The FDA expects that the therapeutic sponsor will address the need for an IVD companion diagnostic device in its therapeutic product development plan and that, in most cases, the therapeutic product and its corresponding IVD companion diagnostic device will be developed contemporaneously. If the companion diagnostic test will be used to make critical treatment decisions such as patient selection, treatment assignment, or treatment arm, it will likely be considered a significant risk device for which a clinical trial will be required. After approval, the use of an IVD companion diagnostic device with a therapeutic product will be stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product. In addition, a diagnostic test that was approved through the PMA process, or one that was cleared through the 510(k) process or reclassified through the *de novo* process, and placed on the market will be subject to many of the same regulatory requirements that apply to approved drugs.

However, the FDA may decide that it is appropriate to approve such a therapeutic product without an approved or cleared *in vitro* companion diagnostic device when the drug or therapeutic biologic is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the FDA determines that the benefits from the use of a product with an unapproved or uncleared *in vitro* companion diagnostic device are so pronounced as to outweigh the risks from the lack of an approved or cleared *in vitro* companion diagnostic device. The FDA encourages sponsors considering developing a therapeutic product that requires a companion diagnostic to request a meeting with both relevant device and therapeutic product review divisions to ensure that the product development plan will produce sufficient data to establish the safety and effectiveness of both the therapeutic product and the companion diagnostic. Because the FDA's policies on companion diagnostics is set forth only in guidance, this policy is subject to change and is not legally binding.

European Union Regulation of Drug Products

In addition to regulations in the United States, we are and will be subject, either directly or through our distribution partners, to a variety of regulations in other jurisdictions governing, among other things, clinical trials, the privacy of personal data and commercial sales and distribution of our products, if approved.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in non-U.S. countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a process that requires the submission of a clinical trial application much like an IND prior to the commencement of human clinical trials. In Europe, for example, a clinical trial application ("CTA"), must be submitted to the competent national health authority and to independent ethics committees in each country in which a company plans to conduct clinical trials. Once the CTA is approved in accordance with a country's requirements, clinical trials may proceed in that country.

The requirements and process governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country, even though there is already some degree of legal harmonization in the European Union member states resulting from the

national implementation of underlying E.U. legislation. In all cases, the clinical trials are conducted in accordance with GCP and other applicable regulatory requirements.

To obtain a marketing license for a new drug, or medicinal product in the European Union, the sponsor must obtain approval of a marketing authorization application ("MAA"). The way in which a medicinal product can be approved in the European Union depends on the nature of the medicinal product. As of January 31, 2020, the United Kingdom (UK) is no longer a member state of the EU, and therefore a separate MAA and approval will be required to market a medicinal product in the UK.

The centralized procedure results in a single marketing authorization granted by the European Commission that is valid across the European Union, as well as in Iceland, Liechtenstein, and Norway. The centralized procedure is compulsory for human drugs that are: (i) derived from biotechnology processes, such as genetic engineering, (ii) contain a new active substance indicated for the treatment of certain diseases, such as HIV/AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune and other immune dysfunctions and viral diseases, (iii) officially designated "orphan drugs" (drugs used for rare human diseases) and (iv) advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines. The centralized procedure may at the request of the applicant also be used for human drugs which do not fall within the above mentioned categories if the human drug (a) contains a new active substance which was not authorized in the European Community; or (b) the applicant shows that the medicinal product constitutes a significant therapeutic, scientific or technical innovation or that the granting of authorization in the centralized procedure is in the interests of patients or animal health at the European Community level.

Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of a marketing authorization application by the European Medicines Agency, or EMA, is 210 days (excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the Committee for Medicinal Products for Human Use, or CHMP), with adoption of the actual marketing authorization by the European Commission thereafter. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest from the point of view of therapeutic innovation, defined by three cumulative criteria: the seriousness of the disease to be treated; the absence of an appropriate alternative therapeutic approach, and anticipation of exceptional high therapeutic benefit. In this circumstance, EMA ensures that the evaluation for the opinion of the CHMP is completed within 150 days and the opinion issued thereafter.

The mutual recognition procedure, or MRP, for the approval of human drugs is an alternative approach to facilitate individual national marketing authorizations within the European Union. Basically, the MRP may be applied for all human drugs for which the centralized procedure is not obligatory. The MRP is applicable to the majority of conventional medicinal products, and is based on the principle of recognition of an already existing national marketing authorization by one or more member states. In the MRP, a marketing authorization for a drug already exists in one or more member states of the European Union and subsequently marketing authorization applications are made in other European Union member states by referring to the initial marketing authorization. The member state in which the marketing authorization was first granted will then act as the reference member state. The member states where the marketing authorization is subsequently applied for act as concerned member states. After a product assessment is completed by the reference member state, copies of the report are sent to all member states, together with the approved summary of product characteristics, labeling and package leaflet. The concerned member states then have 90 days to recognize the decision of the reference member state and the summary of product characteristics, labeling and package leaflet. National marketing authorizations within individual member states shall be granted within 30 days after acknowledgement of the agreement

Should any member state refuse to recognize the marketing authorization by the reference member state, on the grounds of potential serious risk to public health, the issue will be referred to a coordination group. Within a timeframe of 60 days, member states shall, within the coordination group, make all efforts to reach a consensus. If this fails, the procedure is submitted to an EMA scientific committee for arbitration. The opinion of this EMA committee is then forwarded to the Commission, for the start of the decision-making process. As in the centralized procedure, this process entails consulting various European Commission Directorates General and the Standing Committee on Human Medicinal Products or Veterinary Medicinal Products, as appropriate.

Rest of World Government Regulation

For countries outside of the United States and the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, again, the clinical trials are conducted in accordance with GCP and the other applicable regulatory requirements.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension of clinical trials, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions, and criminal prosecution.

Other Healthcare Laws

Although we currently do not have any products on the market, if our product candidates are approved in the United States, we will have to comply with various U.S. federal and state laws, rules and regulations pertaining to healthcare fraud and abuse, including anti-kickback laws and physician self-referral laws, rules and regulations. Violations of the fraud and abuse laws are punishable by criminal and civil sanctions, including, in some instances, exclusion from participation in federal and state healthcare programs, including Medicare and Medicaid. These laws include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made, in whole or in part, under a federal healthcare program such as Medicare and Medicaid;
- the federal False Claims Act imposes civil penalties, and provides for civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;
- the federal transparency requirements under the Physician Payments Sunshine Act require manufacturers of FDA-approved drugs, devices, biologics and medical supplies covered by Medicare or Medicaid to report, on an annual basis, to the Department of Health and Human Services information related to payments and other transfers of value to physicians, teaching hospitals, and certain advanced non-physician health care practitioners and physician ownership and investment interests; and
- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by nongovernmental third-party payors, including private insurers.

Some state laws require pharmaceutical or medical device companies to comply with the relevant industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other health care providers or marketing expenditures.

In November 2020, the Department of Health and Human Services ("DHHS") finalized significant changes to the regulations implementing the Anti-Kickback Statute, as well as the Physician Self-Referral Law (Stark Law) and the civil monetary penalty rules regarding beneficiary inducements, with the goal of offering the healthcare industry more flexibility and reducing the regulatory burden associated with those fraud and abuse laws, particularly with respect to value-based arrangements among industry participants. As noted below under "Healthcare Reform," however, those final rules may be potentially overturned under the Congressional Review Act following the change in control of the legislative and executive branches in January 2021.

State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts. We also may be subject to, or may in the future become subject to, U.S. federal and state, and foreign laws and regulations imposing obligations on how we collect, use, disclose, store and process personal information. Our actual or perceived failure to comply with such obligations could result in liability or reputational harm and could harm our business. Ensuring compliance with such laws could also impair our efforts to maintain and expand our customer base and thereby decrease our future revenues.

Pharmaceutical Coverage, Pricing, and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Sales of our products, when and if approved for marketing in the United States, will depend, in part, on the extent to which our products will be covered by third-party payors, such as federal, state, and foreign government healthcare programs, commercial insurance and managed healthcare organizations. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third-party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the approved products for a particular indication. In addition, these third-party payors are increasingly reducing reimbursements for medical products, drugs and services. Furthermore, the U.S. government, state legislatures and foreign governments have continued implementing cost containment programs, including price controls, restrictions on coverage and reimbursement and requirements for substitution of generic products. Adoption of price controls and cost containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results. Limited third-party reimbursement for our product candidates or a decision by a third-party payor not to cover our product candidates could reduce physician usage of our products once approved and have a material adverse effect on our sales, results of operations and financial condition.

In Europe and other countries outside of the United States, pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed to. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies. In some countries, cross-border imports from low-priced markets exert competitive pressure that may reduce pricing within a country. Any country that has price controls or reimbursement limitations for drug products may not allow favorable reimbursement and pricing arrangements.

Healthcare Reform

In the United States and some foreign jurisdictions, there have been, and continue to be, several legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of product and therapeutic candidates, restrict or regulate post-approval activities, and affect the ability to profitably sell product and therapeutic candidates that obtain marketing approval. The FDA's and other regulatory authorities' policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product and therapeutic candidates. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we otherwise may have obtained and we may not achieve or sustain profitability, which would adversely affect our business, prospects, financial condition and results of operations. Moreover, among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access.

For example, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the ACA, was enacted in March 2010 and has had a significant impact on the health care industry in the U.S. The ACA expanded coverage for the uninsured while at the same time containing overall healthcare costs. With regard to biopharmaceutical products, the ACA, among other things, 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 manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations, established annual fees on manufacturers of certain branded prescription drugs, and created a new Medicare Part D coverage gap discount program. Additionally, on December 20, 2019, President Trump signed the Further Consolidated Appropriations Act for 2020 into law (P.L. 116-94) that includes a piece of bipartisan legislation called the Creating and Restoring Equal Access to Equivalent Samples Act of 2019 or the "CREATES Act." The CREATES Act aims to address the concern articulated by both the FDA and others in the industry that some brand manufacturers have improperly restricted the distribution of their products, including by invoking the existence of a REMS for certain products, to deny generic product developers access to samples of brand products. Because generic product developers need samples to conduct certain comparative testing required by the FDA, some have attributed the inability to timely obtain samples as a cause of delay in the entry of generic products. To remedy this concern, the CREATES Act establishes a private cause of action that permits a generic product developer to sue the brand manufacturer to compel it to furnish the necessary samples on "commercially reasonable, market-based terms." Whether and how generic product developments will use this new pathway, as well as the likely outcome of any legal challenges to provisions of the CREATES Act, remain highly uncertain and its potential effects on future competition for COSELA or any of our other future commercial products are unknown.

As another example, the 2021 Consolidated Appropriations Act signed into law on December 27, 2020 incorporated extensive healthcare provisions and amendments to existing laws, including a requirement that all manufacturers of drugs and biological products covered under Medicare Part B report the product's average sales price, or ASP, to DHHS beginning on January 1, 2022, subject to enforcement via civil money penalties.

Since its enactment, there have been executive, judicial and Congressional challenges to certain aspects of the ACA and we expect there will be additional challenges and amendments to the ACA in the future. Members of the US Congress have indicated that they may continue to seek to modify, repeal or otherwise invalidate all, or certain provisions of, the ACA. For example, the Tax Cuts and Jobs Act, or TCJA, was enacted in 2017 and, among other things, removed penalties, starting January 1, 2019, for not complying with the ACA's individual mandate to carry health insurance, commonly referred to as the "individual mandate." In December 2018, a U.S. District Court Judge in the Northern District of Texas ruled that the individual mandate was a critical and inseverable feature of the ACA, and therefore, because it was repealed as part of the TCJA, the remaining provisions of the ACA were invalid and the law in its entirety was unconstitutional. In December 2019, the U.S. Court of Appeals for the Fifth Circuit upheld the District Court ruling that the individual mandate was unconstitutional but remanded the case back to the District Court to determine whether other reforms enacted as part of the ACA but not specifically related to the individual mandate or health insurance could be severed from the rest of the ACA so as not to be declared invalid as well. On March 2, 2020, the United States Supreme Court granted the petitions for writs of certiorari to review this case and allocated one hour for oral arguments, which occurred on November 10, 2020. A decision from the Supreme Court is expected to be issued in spring 2021. It is unclear how this litigation and other efforts to repeal and replace the ACA will impact the implementation of the ACA, the pharmaceutical industry more generally, and our business. Complying with any new legislation or reversing changes implemented under the ACA could be time-intensive and expensive, resulting in a material adverse effect on our business.

In addition, other legislative changes have been proposed and adopted in the United States since the ACA that affect health care expenditures. These changes include aggregate reductions to Medicare payments to providers of up to 2% per fiscal year pursuant to the Budget Control Act of 2011, which began in 2013 and will remain in effect through 2030 unless additional Congressional action is taken. The Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act, which was signed into law on March 27, 2020 and was designed to provide financial support and resources to individuals and businesses affected by the COVID-19 pandemic, suspended the 2% Medicare sequester from May 1, 2020 through December 31, 2020, and extended the sequester by one year, through 2030, in order to offset the added expense of the 2020 cancellation. The 2021 Consolidated Appropriations Act was subsequently signed into law on December 27, 2020 and extends the CARES Act suspension period to March 31, 2021.

Moreover, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. DHHS, has solicited feedback on some of various measures intended to lower drug prices and reduce the out of pocket costs of drugs and implemented others under its existing authority. For example, in May 2019, DHHS issued a final rule to allow Medicare Advantage plans the option to use step therapy for Part B drugs beginning January 1, 2020. This final rule codified a DHHS policy change that was effective January 1, 2019. As part of the Trump Administration's so-called "Blueprint" to lower drug prices, DHHS and FDA also released on July 31, 2019 their Safe Importation Action Plan proposing two different pathways for the importation of foreign drug products. One pathway focuses on the importation of certain drugs from Canada, which required the agencies to go through notice-and-comment rulemaking, while the second pathway allows manufacturers to distribute their drugs manufactured abroad and was released as agency policy in an FDA guidance document first issued in December 2019. FDA's notice of proposed rulemaking to implement a system whereby state governmental entities could lawfully import and distribute prescription drugs sourced from Canada was published at the end of December 2019 and in September 2020, the rulemaking was finalized by FDA. Those new regulations became effective on November 30, 2020, although the impact of such future programs is uncertain, in part because lawsuits have been filed challenging the government's authority to promulgate them. The final regulations may also be vulnerable to being overturned by a joint resolution of disapproval from Congress under the procedures set forth in the Congressional Review Act, which could be applied to regulatory actions taken by the Trump Administration on or after August 21, 2020 (i.e., in the last 60 days of legislative session of the 116th Congress). Congress and the executive branch have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs, making this area subject to ongoing uncertainty. In addition, the probability of success of other policies enacted over the final months of the Trump Administration and their impact on the U.S. prescription drug marketplace is unknown. There are likely to be political and legal challenges associated with implementing these reforms as they are currently envisioned, and the January 20, 2021 transition to a new Democrat-led presidential administration created further uncertainty. Following his inauguration, President Biden took immediate steps to order a regulatory freeze on all pending substantive executive actions in order to permit incoming department and agency heads to review whether questions of fact, policy, and law may be implicated and to determine how to proceed.

Individual states in the United States have also increasingly passed legislation and implemented regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In December 2020, the U.S. Supreme Court held unanimously that federal law does not preempt the states' ability to regulate pharmaceutical benefit managers (PBMs) and other members of the health care and pharmaceutical supply chain, an important decision that may lead to further and more aggressive efforts by states in this area.

We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, including COSELA and any future products for which we secure marketing approval.

Manufacturing Requirements

We and our third-party manufacturers must comply with applicable cGMP requirements. The cGMP requirements include requirements relating to, among other things, organization of personnel, buildings and facilities, equipment, control of components and drug product containers and closures, production and process controls, packaging and labeling controls, holding and distribution, laboratory controls, records and reports, and returned or salvaged products. The manufacturing facilities for our products must meet cGMP requirements to the satisfaction of the FDA pursuant to a pre-approval inspection before we can use them to manufacture commercial products. We and our third-party manufacturers are also subject to periodic announced or for-cause unannounced inspections of facilities by the FDA and other authorities, including procedures and operations used in the testing and manufacture of our commercial products, if any, to assess our compliance with applicable regulations. Failure to comply with statutory and regulatory requirements subjects a manufacturer to possible legal or regulatory action, including, among other things, warning or other enforcement letters, voluntary corrective action, the seizure of products, injunctions, consent decrees placing significant restrictions on or suspending manufacturing operations, disgorgement of profits, and other civil and criminal penalties.

Other Regulatory Requirements

We are also subject to various laws and regulations regarding laboratory practices, the experimental use of animals, and the use and disposal of hazardous or potentially hazardous substances in connection with our research. In each of these areas, as above, the FDA has broad regulatory and enforcement authority, including, among other things, the ability to levy fines and civil penalties, suspend or delay issuance of approvals, seize or recall products, and withdraw approvals, any one or more of which could have an adverse effect on our ability to operate our business and generate revenues. Compliance with applicable environmental laws and regulations is expensive, and current or future environmental regulations may impair our research, development and production efforts, which could harm our business, operating results and financial condition.

Human Capital Management

As of December 31, 2020, we employed 220 employees, of which 217 were full-time employees. A significant number of our management and professional employees have had prior experience with pharmaceutical, biotechnology or medical product companies. None of our employees are represented by a labor union or covered under a collective bargaining agreement. Management considers relations with our employees to be good.

Our approach to human capital management is driven by our values statement: Making an impact through innovation, inclusion, and inspiration. Our values are at the core of who we are as an organization, and what drive us to envision a brighter future for the patients and families affected by genetically defined diseases. In order for us to build a world-class organization to develop a new era of nucleic acid medicines, we must build and maintain an exceptional team in which each member plays a unique and important role, and embrace a forward-thinking philosophy that extends beyond our work, to how we are building our culture and benefits.

We recognize that maintaining an engaged and top-notch workforce and a connection with the communities we serve is critical to our success. Comradery and cohesion are at the core of who we are as a company and are integral facets of our human capital management strategy. Whether it is coming together throughout the year to connect at our town halls or participating in a global fitness challenge to support the health and well-being of our employees, we take a team approach to our work. We are inspired by each other and the possibilities of what we can achieve together.

We understand that in order to drive innovation, we must continuously improve our human capital management strategies and find ways to foster engagement and growth within our organization. To this end, below are some of our initiatives:

Employee Engagement: Having an engaged and dedicated workforce is essential for us to achieve our goals. Employee engagement ensures that our employees feel passionate about the work they are doing, and with this commitment, we recognize that this is when results happen. It is more apparent than ever that we are all in this together, and as a company, we need to set up our employees for success and continue to cultivate their engagement with our company. We conduct an annual employee engagement survey as a means of measuring employee engagement and satisfaction, as well as a tool for improving our human capital strategies in the year ahead. Engagement is also directly correlated to the interactions our employees have with each other and their teams. Our Wave Activities Committee is a cross-functional team dedicated to organizing activities, such as themed social gatherings, charity and volunteer opportunities, and health and wellness events, that enrich our culture and bring employees together. We also work to ensure that we

are deeply aligned on our corporate goals as a company, that functional goals are clear and transparent, and employees understand how their work contributes to the company's success.

Employee Health and Safety: Compliance with environmental, health and safety ("EH&S") laws and regulations underlies the basis of the EH&S programs we have in place. As we continue to monitor the global spread of COVID-19, we have implemented and will continue to implement measures to ensure the safety of our employees and our patients. We formed a COVID-19 Response Team, which is continuously evaluating the guidance from federal and local authorities and has created strict polices and guidelines that put our employee's health and safety first. The EH&S management system incorporates processes to proactively assess risks to the health and safety of our employees and the community, as well as tracking compliance, incidents, inspections, and corrective actions. Our training program provides enhanced training to individuals that is parallel to the level of risk exposure to ensure that employees always have the knowledge and equipment at hand to mitigate risk.

Professional Development Programs and Opportunities: Our greatest asset is our employees and we aspire to provide them with opportunities so they can continue to grow and excel within their field, and our company. Professional growth of our employees leads to engagement and allows us to leverage opportunities so we can hire key talent from within. We have also implemented a personal development plan program, along with leadership and management development programs. Through development planning, we strive for employees at all levels to focus on strengthening the skills required in their current role or a potential future role. We conduct formal annual performance reviews for all employees, but as importantly, we are focused on building a culture of coaching, feedback and open communication between managers and their direct reports throughout the entire year. We provide managers and employees with training on how to conduct effective forward-looking performance conversations and to set effective goals that are realistic, measurable, attainable, relevant and timebound (SMART). Another example where we provide leadership and development opportunities is through the Wave Learning Series, which was developed to build awareness of all functional areas at Wave, and to expand knowledge of industry trends and other matters of interest and relevance within the biopharmaceutical industry. The Wave Learning Series is conducted through company-wide presentations by employees at various levels, providing opportunities for development and cross-functional exposure for our employees. To further assist our employees, we also offer all full-time employees the option to participate in our Education Assistance Program, where we reimburse employees for tuition and eligible expenses.

Health and Well-Being: We believe that the overall well-being of our employees and ensuring that their basic health and wellness needs are met is fundamental for us to achieve success as a company. We provide an Employee Assistance Program ("EAP"), as a cost-free benefit, which is available to help employees and their household members confidentially manage everyday life, work challenges, stress, and other personal issues by providing consultation, referrals and resources. In 2020, in light of the COVID-19 global pandemic, we partnered with our EAP provider to provide a series of virtual meetings where employees could discuss the challenges and successes they have had during these unprecedented times, and discuss the importance of staying resilient while facing uncertainty.

Diversity and Inclusion: Our commitment to maintaining a top-performing company means investing in and creating ongoing opportunities for employee development in a diverse and inclusive environment. We believe that a diverse workforce not only positively impacts our performance, fosters innovation, inspires us to achieve greater results, increases our collective capabilities and strengthens our culture, but it also cultivates an essential pipeline of experienced leaders for management. Hiring for diversity of thought, background and experience, and diversity of personal characteristics such as gender, race and ethnicity is intentional at Wave and continues to be an area of focus as we build our workforce. Despite the historical lack of institutional emphasis on the importance of girls and women focusing on education in science, technology, engineering and mathematics ("STEM") and the resulting disproportionate occupation by men in the STEM-educated talent pool, the Company has prioritized and hired a gender diverse workforce. As of December 31, 2020, women make up approximately 51% of our global workforce and constitute approximately 43% of management. We are also committed to building a racially and ethnically diverse workforce. As of December 31, 2020, racially diverse employees (those self-identifying as Black or African American, Hispanic or Latino, Asian, or being two or more races) make up approximately 42% of our global workforce and approximately 21% of management (12% of our employees did not provide us with this information).

Community Outreach and Engagement: Our community engagement activities are focused on seeking to better understand the lives of people living with rare disease and identifying opportunities to support the rare disease community. We believe that partnering with and understanding the lives of patients and their families differentiates Wave and enhances our ability to discover and develop potential therapies. Through collaboration with patients, families and advocacy organizations, face-to-face meetings, and participation in patient-focused conferences and community events, we aim to broaden our understanding of the needs of patients and families and incorporate those critical learnings into every aspect of our company. These insights inform the design and execution of our clinical trials, the enrichment of our corporate culture, and the development of programs and services that make a positive impact on people's lives. Employee volunteerism is another important component of our community engagement initiatives. We partner with advocacy and service organizations to provide opportunities for employees to contribute directly to our local communities. By participating in a broad range of volunteer activities, our employees donate time and resources to support patients and families in the rare disease community.

Rewards and Recognition: We have a multi-tiered awards programs, including peer-to-peer recognition, that our employees use to recognize and reward one another for their contributions and achievements, taking into consideration the combination of employees who best exemplify our values and the achievement of results. We believe that providing a rewards program not only increases engagement and performance, but meaningfully recognizes those employees who go above and beyond to positively impact our company and culture.

Compensation, Equity and Benefits: We have designed a broad-based compensation program that is designed attract, retain and motivate our employees to deliver sustainable long-term value. We seek to deliver performance-driven, market competitive reward opportunities commensurate with company and individual performance. All employees of Wave receive base salaries, cash bonuses, new hire equity grants and annual long-term incentive grants, in addition to our generous benefits package. We believe that providing employees with an ownership interest in the Company will further strengthen the level of employee engagement. Furthermore, equity awards help align the interests of our employees with the long-term interests of our shareholders. In addition, we have an Employee Stock Purchase Plan ("ESPP"), which provides our employees with an opportunity to purchase shares of our Company at a 15% discount to the market price.

Offering a highly competitive, industry-leading, benefits package is another integral piece of our compensation program. Notably, we provide our employees with access to choice and offer employees a very progressive health insurance package, with no premiums. We also maintain a 401(k) plan with matching contributions that all of our employees are eligible to participate in.

We will continue to evolve and strengthen our human capital management strategies, while furthering our investment in our employees, culture, community partnerships and outreach, and other human capital measures.

Corporate Information

We were incorporated under the name Wave Life Sciences Pte. Ltd. (Registration No.: 201218209G) under the laws of Singapore on July 23, 2012. On November 16, 2015, we closed our initial public offering. In preparation for our initial public offering, on November 5, 2015, Wave Life Sciences Pte. Ltd. converted from a private limited company to a public limited company known as Wave Life Sciences Ltd. ("Wave"). Wave has four wholly-owned subsidiaries: Wave Life Sciences USA, Inc. ("Wave USA"), a Delaware corporation (formerly Ontorii, Inc.); Wave Life Sciences Japan, Inc. ("Wave Japan"), a company organized under the laws of Japan (formerly Chiralgen., Ltd.); Wave Life Sciences Ireland Limited ("Wave Ireland"), a company organized under the laws of Ireland; and Wave Life Sciences UK Limited ("Wave UK"), a company organized under the laws of the United Kingdom.

Our registered office is located at 7 Straits View #12-00, Marina One East Tower, Singapore 018936, and our telephone number at that address is +65 6236 3388. Our principal office for Wave USA is located at 733 Concord Avenue, Cambridge, MA 02138, and our telephone number at that address is +1-617-949-2900. Our registered office for Wave Japan is 2438 Miyanoura-cho, Kagoshima-shi, Kagoshima pref. 891-1394, Japan. Our registered office for Wave Ireland is One Spencer Dock, North Wall Quay, Dublin 1, D01 X9R7, Ireland. Our registered office for Wave UK is 1 Chamberlain Square CS, Birmingham B3 3AX, United Kingdom.

Information Available on the Internet

Our Internet website address is http://www.wavelifesciences.com. The information contained on, or that can be accessed through, our website is not a part of, or incorporated by reference in, this Annual Report on Form 10-K. We have included our website address in this Annual Report on Form 10-K solely as an inactive textual reference. We make available free of charge through our website our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Exchange Act. We make these reports available through the "For Investors & Media – Financial Information" section of our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the Securities and Exchange Commission ("SEC"). We also make available, free of charge on our website, the reports filed with the SEC by our executive officers, directors and 10% shareholders pursuant to Section 16 under the Exchange Act as soon as reasonably practicable after copies of those filings are filed with the SEC. You can review our electronically filed reports and other information that we file with the SEC on the SEC's website at http://www.sec.gov.

In addition, we regularly use our website to post information regarding our business and governance, and we encourage investors to use our website, particularly the information in the section entitled "For Investors & Media," as a source of information about us.

Item 1A. Risk Factors

Risk Factors

You should carefully consider the following risk factors, in addition to the other information contained in this Annual Report on Form 10-K, including the section of this report titled "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our financial statements and related notes. If any of the events described in the following risk factors and the risks described elsewhere in this Annual Report on Form 10-K occurs, our business, operating results and financial condition could be seriously harmed and the trading price of our ordinary shares could decline. This Annual Report on Form 10-K also contains forward-looking statements that involve risks and uncertainties. Our actual results could differ materially from those anticipated in the forward-looking statements as a result of factors that are described below and elsewhere in this Annual Report on Form 10-K.

Risks Related to Our Financial Results and Capital Requirements

We are a clinical-stage genetic medicines company with a history of losses, and we expect to continue to incur losses for the foreseeable future, and we may never achieve or maintain profitability.

We are a clinical-stage genetic medicines company and have incurred significant operating losses since our incorporation in 2012. Our net loss was $149.9 million and $193.6 million for the fiscal years ended December 31, 2020 and 2019, respectively. As of December 31, 2020 and 2019, we had an accumulated deficit of $683.3 million and $533.4 million, respectively. To date, we have not generated any product revenue. Substantially all of our losses have resulted from expenses incurred in connection with our research and development programs and from general and administrative costs associated with our operations. We currently have no products on the market and expect that it may be many years, if ever, before we have a product candidate ready for commercialization. We are conducting clinical trials of our two most advanced programs in HD and expect to deliver data from those trials at the end of the first quarter of 2021. Also in 2021, we expect to initiate dosing in three new clinical trials with compounds containing our novel PN backbone chemistry modifications, including WVE-003 in HD, WVE-004 in ALS and FTD, and WVE-N531 in DMD. Beyond neurology, we are advancing our first ADAR editing program in alpha-1 antitrypsin disorders. We are also evaluating our ophthalmology programs and continue to explore additional targets in neurology and hepatic disorders.

We have not generated, and do not expect to generate, any product revenue for the foreseeable future, and we expect to continue to incur significant operating losses for the foreseeable future due to the cost of research and development, manufacturing, preclinical studies and clinical trials and the regulatory review process for product candidates. The amount of future losses is uncertain. To achieve profitability, we must successfully develop product candidates, obtain regulatory approvals to market and commercialize product candidates, manufacture any approved product candidates on commercially reasonable terms, establish a sales and marketing organization or suitable third-party alternatives for any approved product and raise sufficient funds to finance our business activities. We may never succeed in these activities and, even if we do, may never generate revenues that are significant or large enough to achieve profitability. 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, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our company could also cause our shareholders to lose all or part of their investment.

We will require substantial additional funding, which may not be available on acceptable terms, or at all.

We have used substantial funds to develop our programs and PRISM, our proprietary discovery and drug development platform, and will require substantial funds to conduct further research and development, including preclinical studies and clinical trials of our product candidates, seek regulatory approvals for our product candidates and manufacture and market any products that are approved for commercial sale. We believe that our existing cash and cash equivalents will be sufficient to fund our operations for at least the next 12 months.

Our future capital requirements and the period for which we expect our existing resources to support our operations may vary significantly from what we expect. We do not expect to realize any appreciable revenue from product sales or royalties in the foreseeable future, if at all. Our revenue sources will remain extremely limited unless and until our product candidates complete clinical development and are approved for commercialization and successfully marketed. Because we cannot be certain of the length of time or activities associated with successful development and commercialization of our product candidates, we are unable to estimate the actual funds we will require to develop and commercialize them.

Our future capital requirements will depend on many factors, including, but not limited to, the following:

- our monthly spending levels, based on new and ongoing development and corporate activities;
- the scope, progress, results and costs of drug discovery, preclinical and clinical development for our product candidates;

- our ability to establish and maintain collaboration arrangements, and whether our collaboration partners decide to exercise option rights in connection with targets and development programs;
- the costs, timing and outcome of regulatory review of our product candidates;
- our ability to obtain marketing approval for our product candidates;
- the impacts of the COVID-19 global pandemic (and emerging or future variants of COVID-19) on our business;
- the achievement of milestones and other development targets that trigger payments under our collaborations with Takeda Pharmaceutical Company Limited ("Takeda"), or any other strategic collaborations into which we may enter;
- the extent to which we are obligated to reimburse, or entitled to reimbursement of, clinical trial costs or expenses and other costs and expenses associated with research and preclinical and clinical activities under our collaboration with Takeda, or any other future collaboration agreements, if any;
- the costs and timing of future commercialization activities, including manufacturing, marketing, sales and distribution, for any of our product candidates for which we receive marketing approval;
- market acceptance of our product candidates, to the extent any are approved for commercial sale, and the revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims;
- the costs of securing manufacturing arrangements internally or with third parties for drug supply.

To date, we have primarily financed our operations through sales of our securities and our collaborations with third parties. As a privately held company, we received an aggregate of $89.3 million from the sale of our securities. As a publicly traded company, through March 3, 2021, we have received an aggregate of $484.5 million in gross proceeds from public offerings of our securities, or approximately $449.4 million in net proceeds, including gross proceeds of $111.9 million from our November 2015 initial public offering, $100.0 million from our April 2017 follow-on public offering, $172.6 million from our January 2019 follow-on public offering, and $100.0 million from our September 2020 follow-on public offering. On March 2, 2020, we filed a post-effective amendment to our registration statement on Form S-3 (the "Registration Statement") because we no longer qualified as a "well-known seasoned issuer" as such term is defined in Rule 405 of the Securities Act of 1933, as amended. The Registration Statement includes a base prospectus covering the offering, issuance and sale of up to $340.0 million in the aggregate of our ordinary shares, debt securities, warrants, and rights, separately or as units or any combination thereof, in one or more offerings. The Registration Statement also includes a prospectus covering up to an aggregate of $190.0 million in ordinary shares that we may issue and sell from time to time, through Jefferies LLC acting as our sales agent, pursuant to the open market sales agreement that we entered into with Jefferies LLC in May 2019 for our at-the-market equity program. As of March 3, 2021, we have received $60.9 million in gross proceeds from our at-the-market equity program under the sales agreement prospectus pursuant to the Registration Statement. In addition, we have received $40.0 million under our collaboration with Pfizer and received (or are due to receive) an aggregate of $230.0 million in equity investments, upfront and committed payments under our collaboration with Takeda, exclusive of any potential future milestone and royalty payments. We intend to seek additional funding in the future through collaborations, public or private equity offerings or debt financings, credit or loan facilities or a combination of one or more of these financing sources.

Our ability to raise additional funds will depend on financial, economic and other factors, many of which are beyond our control. For example, in connection with our data readouts in December 2019, our stock price declined significantly, which may make it more difficult for us to obtain additional funding on terms as favorable as those prior to our stock price decline. Additional funds may not be available to us on acceptable terms or at all. If we raise additional funds by issuing equity or convertible debt securities, our shareholders will suffer dilution and the terms of any financing may adversely affect the rights of our shareholders. In addition, as a condition to providing additional funds to us, future investors may demand, and may be granted, rights superior to those of existing shareholders. Debt financing, if available, may involve restrictive covenants limiting our flexibility in conducting future business activities, and, in the event of insolvency, debt holders would be repaid before holders of equity securities received any distribution of corporate assets.

If we are unable to obtain funding on a timely basis or on acceptable terms, we may have to delay, limit or terminate our research and development programs and preclinical studies or clinical trials, limit strategic opportunities or undergo reductions in our workforce or other corporate restructuring activities. We also could be required to seek funds through arrangements with collaborators or others that may require us to relinquish rights to some of our product candidates or technologies that we would otherwise pursue on our own.

Our management has broad discretion over the use of proceeds received from sales of our securities and our collaborations with third parties and the proceeds may not be used effectively.

Our management has broad discretion as to the use of proceeds we receive from conducting sales of our securities and our collaborations with third parties and could use the proceeds for purposes other than those contemplated at the time of such transactions. It is also possible that the proceeds we have received, or may receive, from securities sales and collaborations will be invested in a way that does not yield a favorable, or any, return for us.

Our short operating history may make it difficult for shareholders to evaluate the success of our business to date and to assess our future viability.

We are a clinical-stage genetic medicines company with a limited operating history. We commenced active operations in 2012. Our operations to date have been limited to organizing and staffing our company, research and development activities, manufacturing, preclinical and clinical development, patient advocacy activities, business planning and raising capital. Prior to 2017, all of our product candidates were in the preclinical development stage. We are conducting clinical trials of our two most advanced programs in HD and expect to deliver data from those trials at the end of the first quarter of 2021. Also in 2021, we expect to initiate dosing in three new clinical trials with compounds containing our novel PN backbone chemistry modifications, including WVE-003 in HD, WVE-004 in ALS and FTD, and WVE-N531 in DMD. Beyond neurology, we are advancing our first ADAR editing program in alpha-1 antitrypsin disorders. We are also evaluating our ophthalmology programs and continue to explore additional targets in neurology and hepatic disorders. We have not yet demonstrated our ability to successfully complete pivotal clinical trials, obtain marketing approvals, or conduct sales and marketing activities necessary for successful product commercialization. We have limited experience manufacturing our products at commercial scale or arranging for a third party to do so on our behalf. Typically, it takes many years to develop and commercialize a therapeutic from the time it is discovered to when it is available for treating patients. Further, drug development is a capital-intensive and highly speculative undertaking that involves a substantial degree of risk. You should consider our prospects in light of the costs, uncertainties, delays and difficulties frequently encountered by biotechnology companies in the early stages of clinical development, such as ours. Any predictions about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successfully developing and commercializing pharmaceutical products.

We, or third parties upon whom we depend, may face risks related to health epidemics, including the novel coronavirus (COVID-19) pandemic and variants thereof, which may delay our ability to complete our ongoing clinical trials, initiate additional clinical trials, delay regulatory activities and have other adverse effects on our business and operations.

Since December 2019, multiple countries throughout the world and their economies, including the United States, have been subject to intermittent shutdowns and adversely affected by the COVID-19 global pandemic. To date, responsive measures such as social distancing, work-from-home policies, travel bans and quarantines have been implemented in many countries throughout the world, including the United States. We are in the midst of the global pandemic; therefore, we are continuing to evaluate the situation and the extent to which these responsive measures may materially and adversely affect our business operations and financial condition.

As a clinical-stage company with multiple programs and multiple clinical trials currently underway, the pandemic is impacting the execution of our clinical trials. We have clinical trial sites located in countries that have been affected by COVID-19 and variants thereof. Clinical site initiation and patient enrollment has been delayed due to prioritization of hospital resources in favor of COVID-19 patients and difficulties in recruiting clinical site investigators and clinical site staff. Some patients have not be able to comply with clinical trial protocols caused by quarantines impeding patient movement and interrupting healthcare services, or patients may not be willing to travel to clinical trial sites. Similarly, our ability to recruit and retain patients and principal investigators and site staff who, as healthcare providers, may have heightened risk of exposure to COVID-19, has been negatively impacted, which has delayed the timelines of our clinical trial operations. We are continuing to experience delays and disruptions in our clinical trials and preclinical studies due to resource constraints at contract research organizations and vendors along their supply chain. We may also experience interruption of key clinical trial activities, such as clinical trial site data monitoring, due to limitations on travel imposed or recommended by federal or state governments, employers and others or interruption of clinical trial subject visits and study procedures (particularly any procedures that may be deemed non-essential), which may impact the integrity of subject data and clinical trial endpoints.

The COVID-19 pandemic has affected and may continue to affect the operations of the FDA, EMA and other regulatory authorities, which could result in delays of reviews and approvals, including with respect to our product candidates. If regulatory matters resulting from COVID-19 continue to prevent regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities, it could impact the ability of regulatory authorities to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

We rely upon third parties for many aspects of our business, including the raw materials used to make our product candidates and the conduct of our clinical trials and preclinical studies. While we have built up inventory to assist us through this uncertain operating environment, our suppliers may be disrupted now or in the future, which may affect our ability to procure items that are essential for our research and development activities and may cause significant disruptions to our business.

We have implemented procedures to protect our workforce in manufacturing and laboratory operations while ensuring appropriate remote working protocols have been implemented for our employees who can work from home. The spread of COVID-19 and the responsive measures taken to date have limited our access to our facilities and caused the majority of our employees to work from home. We continue to monitor the global spread of COVID-19 and the response of international, national and local authorities, and

have implemented and will continue to implement measures that we believe are appropriate and necessary for our business and the safety of our employees. In response to these public health directives and orders, we have implemented a work-from-home policy for our employees. The effects of the executive order, the stay-at-home advisory and our work-from-home policy may negatively impact productivity, disrupt our business and delay our clinical programs and timelines, the magnitude of which will depend, in part, on the length and severity of the restrictions and other limitations on our ability to conduct our business in the ordinary course. The increase in working remotely has increased our cybersecurity risk, has created data accessibility concerns, and has made us more susceptible to communication disruptions. In addition, as a result of potential shelter-in-place orders or other mandated travel restrictions, our on-site staff conducting research and development and manufacturing activities have experienced difficulties and delays in accessing our laboratories or manufacturing space.

Our future capital requirements depend on many factors, including the continued uncertainty and duration of the COVID-19 pandemic. As a result, we may face difficulties raising capital through sales of our securities or such sales may be on unfavorable terms.

The COVID-19 global pandemic, including any emerging variants of COVID-19, is continuing to evolve rapidly and subject to change. While we are adapting our processes to lessen the impact that COVID-19 may have on our business, we do not yet know the full extent of delays or long-term impacts on our business, our clinical trials, healthcare systems or the global economy. These impacts are highly uncertain and cannot be predicted with confidence, such as variants of the virus that may evolve, the duration of the outbreak, travel restrictions and actions to contain the outbreak or treat its impact, such as social distancing and quarantines or lock-downs in the United States and other countries, business closures or business disruptions and the effectiveness of actions taken in the United States and other countries to contain and treat the disease. These effects may materially adversely affect our business, financial condition, results of operations, and prospects.

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

The approach we are taking to discover and develop oligonucleotides is novel and may never lead to marketable products.

We have concentrated our efforts and research and development activities on oligonucleotides and enhancing PRISM, our proprietary discovery and drug development platform. PRISM enables us to target genetically defined diseases with stereopure oligonucleotides across multiple therapeutic modalities. Our future success depends on the successful development of stereopure oligonucleotides and the effectiveness of PRISM. The scientific discoveries that form the basis for our efforts to discover and develop new product candidates, including our discoveries about the relationships between oligonucleotide stereochemistry and pharmacology, are relatively new. PRISM combines our unique ability to control backbone stereochemistry to create stereopure oligonucleotides and our deep knowledge of how the interplay among oligonucleotide sequence, chemistry and backbone stereochemistry impacts key properties. The scientific evidence to support the feasibility of developing medicines based on these discoveries is limited. Skepticism as to the feasibility of developing oligonucleotides generally has been, and may continue to be, expressed in scientific literature. In addition, decisions by other companies with respect to their oligonucleotide development efforts may increase skepticism in the marketplace regarding the potential for oligonucleotides.

A number of clinical trials for oligonucleotide products conducted by other companies have not been successful, but some have received regulatory approval. The pharmacological properties ascribed to the investigational compounds we are testing in laboratory studies may not be positively demonstrated in clinical trials in patients, and they may interact with human biological systems in unforeseen, ineffective or harmful ways. For example, in December 2019, we discontinued development of suvodirsen for patients with DMD based on the interim analysis of the Phase 1 open-label extension (OLE) study. If our product candidates prove to be ineffective, unsafe or commercially unviable, PRISM and our pipeline would have little, if any, value, which would substantially harm our business, financial condition, results of operations and prospects. In addition, our approach, which focuses on using oligonucleotides for drug development, as opposed to multiple or other, more advanced proven technologies, and new products and technologies that may enter the market, may expose us to additional financial risks and make it more difficult to raise additional capital if we are not successful in developing one or more oligonucleotides that receive regulatory approval.

Because we are developing oligonucleotides, which are considered a relatively new class of drugs, there is increased risk that the outcome of our clinical trials will not be sufficient to obtain regulatory approval.

The FDA and comparable ex-U.S. regulatory agencies have relatively limited experience with oligonucleotides, which may increase the complexity, uncertainty and length of the regulatory review process for our product candidates. To date, the FDA has approved only 11 oligonucleotides for marketing and commercialization. Even though the FDA in January 2021 issued a draft guidance document relating to IND submissions for individualized antisense oligonucleotide drugs for severely debilitating or life-threatening genetic diseases, the FDA and its foreign counterparts have not yet established any definitive policies, practices or guidelines specifically in relation to the development considerations for these drugs. The general lack of policies, practices or guidelines specific to oligonucleotides may hinder or slow review by the FDA of any regulatory filings that we may submit. Moreover, the FDA may

respond to these submissions by defining requirements we may not have anticipated. Such responses could lead to significant delays in the development of our product candidates. In addition, because there may be approved treatments for some of the diseases for which we may seek approval, in order to receive regulatory approval, we may need to demonstrate through clinical trials that the product candidates we develop to treat these diseases, if any, are not only safe and effective, but safer or more effective than existing products. Furthermore, in recent years, there has been increased public and political pressure on the FDA with respect to the approval process for new drugs, and the FDA's standards, especially regarding drug safety, appear to have become more stringent. As a result of the foregoing factors, we may never receive regulatory approval to market and commercialize any product candidate.

Even if we obtain regulatory approval, the approval may be for disease indications or patient populations that are not as broad as we intended or desired or may require labeling that includes significant use or distribution restrictions or safety warnings. We may be required to perform additional or unanticipated clinical trials to obtain regulatory approval or be subject to additional post-marketing studies or other requirements to maintain such approval. As a result, we may never succeed in developing a marketable product, we may not become profitable and the value of our ordinary shares could decline.

Our preclinical studies and clinical trials may not be successful. If we are unable to commercialize our product candidates or experience significant delays in doing so, our business will be materially harmed.

We are conducting clinical trials of our two most advanced programs in HD and expect to deliver data from those trials at the end of the first quarter of 2021. Also in 2021, we expect to initiate dosing in three new clinical trials with compounds containing our novel PN backbone chemistry modifications, including WVE-003 in HD, WVE-004 in ALS and FTD, and WVE-N531 in DMD. Beyond neurology, we are advancing our first ADAR editing program in alpha-1 antitrypsin disorders. We are also evaluating our ophthalmology programs and continue to explore additional targets in neurology and hepatic disorders. However, we currently have no products on the market. We have invested a significant portion of our efforts and financial resources in the identification and preclinical and clinical development of our oligonucleotides, the development of PRISM and our novel PN backbone chemistry modifications, and the continued growth of our manufacturing capabilities. Our ability to generate product revenue, which we do not expect will occur for many years, if ever, will depend heavily on the successful development and eventual commercialization of our product candidates. Our success will depend on several factors, including the following:

- successfully completing preclinical studies and clinical trials;
- successfully conducting process development and manufacturing campaigns in accordance with current good manufacturing practice ("cGMP");
- receiving regulatory approvals from applicable regulatory authorities to market our product candidates and, to the extent necessary, our companion diagnostic tests;
- establishing commercial manufacturing capabilities or making arrangements with third party contract manufacturing organizations ("CMOs");
- obtaining and maintaining patent and trade secret protection and regulatory exclusivity for our product candidates;
- the degree to which we are successful in our collaboration with Takeda, and any additional collaborations we may establish;
- launching commercial sales of the products, if and when approved, whether alone or in collaboration with others;
- acceptance of the products, if and when approved, by patients, the medical community and third-party payors;
- effectively competing with other therapies; and
- continuing to maintain an acceptable safety profile of the products following approval.

If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our product candidates, which would materially harm our business.

We may not be able to conduct clinical trials successfully due to various process-related factors that could negatively impact our business plans.

The successful initiation and completion of any of our clinical trials, within timeframes consistent with our business plans, is dependent on various factors, which include, but are not limited to, our ability to:

- retain and recruit employees, contractors or consultants with the required level of knowledge and experience;
- retain and recruit in a timely manner a sufficient number of patients necessary to conduct a clinical trial, which is a function of many factors, including the impact of the COVID-19 global pandemic, the proximity of participants to clinical

sites, the size of the relevant population, the eligibility criteria for the trial, possible side effects from treatments, the existence of competing clinical trials, the involvement of patient advocacy groups, the availability of new or alternative treatments, lack of efficacy, personal issues and ease of participation;

- manage the impact of the COVID-19 pandemic on our early-stage discovery efforts and clinical trials;
- open study sites, and enroll, treat, and monitor patients due to local restrictions implemented in response to the COVID-19 or other global health pandemics;
- develop companion diagnostic tests for use with certain of our product candidates;
- manufacture and maintain a sufficient amount of clinical material, internally or through third parties;
- ensure adherence to trial designs and protocols agreed upon and approved by regulatory authorities and applicable regulatory and legal guidelines;
- manage or resolve unforeseen adverse side effects during a clinical trial;
- execute clinical trial designs and protocols approved by regulatory authorities without deficiencies;
- timely and effectively contract with (under reasonable terms), manage and work with investigators, institutions, hospitals and the contract research organizations ("CROs") involved in the clinical trial;
- negotiate contracts and other related documents with clinical trial parties and institutional review boards ("IRBs"), such as informed consents, CRO agreements and site agreements, which can be subject to extensive negotiations that could cause significant delays in the clinical trial process, with terms possibly varying significantly among different trial sites and CROs and possibly subjecting us to various risks; and
- conduct clinical trials in a cost-effective manner, including management of foreign currency risk in clinical trials conducted in foreign jurisdictions and cost increases due to unforeseen or unexpected complications such as enrollment delays, or needing to outsource certain functions during the clinical trial.

If we are not able to manage the clinical trial process successfully, our business plans could be delayed or be rendered unfeasible for us to execute within our planned or required time frames, or at all.

If we cannot successfully manufacture our product candidates for our research and development and preclinical activities, or manufacture sufficient amounts of our product candidates to meet our clinical requirements and timelines, our business may be materially harmed.

In order to develop our product candidates, apply for regulatory approvals and commercialize our product candidates, we will need to develop, contract for, or otherwise arrange for the necessary manufacturing capabilities. In September 2016, we entered into a lease for a multi-use facility of approximately 90,000 square feet in Lexington, Massachusetts to provide internal cGMP manufacturing capabilities and increase control and visibility of our drug substance supply chain, and we began cGMP manufacturing in this facility at the beginning of 2018. This facility supplements our existing Cambridge, Massachusetts laboratory and office space headquarters, enhances our ability to secure drug substance for current and future development activities and may provide commercial-scale manufacturing capabilities. However, while we have established and continue to enhance our internal cGMP manufacturing capabilities, we have limited experience manufacturing drug substance on a commercial scale, and we will incur significant costs to develop this expertise internally.

In addition to the oligonucleotides that we manufacture internally, we continue to utilize CMOs to manufacture the oligonucleotides required for our preclinical studies and clinical trials. There are a limited number of manufacturers that supply oligonucleotides. There are risks inherent in pharmaceutical manufacturing that could affect our ability or the ability of our CMOs to meet our delivery time requirements or provide adequate amounts of material to meet our clinical trial demands on our projected timelines. Included in these risks are potential synthesis and purification failures and/or contamination during the manufacturing process, as well as other issues with our facility or the CMOs' facilities and ability to comply with the applicable manufacturing requirements, which could result in unusable product and cause delays in our manufacturing timelines and ultimately delay our clinical trials, as well as result in additional expense to us. To manufacture our oligonucleotides, we rely on third parties to supply the required raw materials. We will likely need to secure alternative suppliers for these raw materials, and such alternative suppliers are limited and may not be readily available, or we may be unable to enter into agreements with them on reasonable terms and in a timely manner. For example, we source certain materials used in the manufacture of our products from China and other countries outside of the United States; the coronavirus outbreak or other similar global disruptions could make access to our existing supply chain difficult and could impact our business. Additionally, our cost of goods development is at an early stage. The actual cost to manufacture and process our product candidates could be greater than we expect and could materially and adversely affect the commercial viability of our product candidates.

The process of manufacturing oligonucleotides is complex and we may encounter difficulties in production, particularly with respect to process development or scaling-up of our manufacturing capabilities.

The process of manufacturing oligonucleotides is complex, highly-regulated and subject to multiple risks. The complex processes associated with the manufacture of our product candidates expose us to various manufacturing challenges and risks, which may include delays in manufacturing adequate supply of our product candidates, limits on our ability to increase manufacturing capacity, and the potential for product failure and product variation that may interfere with preclinical and clinical trials, along with additional costs. We also may make changes to our manufacturing process at various points during development, and even after commercialization, for various reasons, such as controlling costs, achieving scale, decreasing processing time, increasing manufacturing success rate, or other reasons. Such changes carry the risk that they will not achieve their intended objectives, and any of these changes could cause our product candidates to perform differently and affect the results of current or future clinical trials, or the performance of the product, once commercialized. In some circumstances, changes in the manufacturing process may require us to perform *ex vivo* comparability studies and to collect additional data from patients prior to undertaking more advanced clinical trials. For instance, changes in our process during the course of clinical development may require us to show the comparability of the product used in earlier clinical trials or at earlier portions of a trial to the product used in later clinical trials or later portions of the trial. We may also make further changes to our manufacturing process before or after commercialization, and such changes may require us to show the comparability of the resulting product to the product used in the clinical trials using earlier processes. We may be required to collect additional clinical data from any modified process prior to obtaining marketing approval for the product candidate produced with such modified process. If clinical data are not ultimately comparable to that seen in the earlier trials in terms of safety or efficacy, we may be required to make further changes to our process and/or undertake additional clinical testing, either of which could significantly delay the clinical development or commercialization of the associated product candidate.

We are conducting clinical trials of our two most advanced programs in HD and expect to deliver data from those trials at the end of the first quarter of 2021. Also in 2021, we expect to initiate dosing in three new clinical trials with compounds containing our novel PN backbone chemistry modifications, including WVE-003 in HD, WVE-004 in ALS and FTD, and WVE-N531 in DMD. Beyond neurology, we are advancing our first ADAR editing program in alpha-1 antitrypsin disorders. We are also evaluating our ophthalmology programs and continue to explore additional targets in neurology and hepatic disorders. Although we continue to build on our experience in manufacturing oligonucleotides, we have limited experience as a company manufacturing product candidates for commercial supply. We may never be successful in manufacturing product candidates in sufficient quantities or with sufficient quality for commercial use. Our manufacturing capabilities could be affected by cost-overruns, unexpected delays, equipment failures, labor shortages, operator error, natural disasters, unavailability of qualified personnel, difficulties with logistics and shipping, problems regarding yields or stability of product, contamination or other quality control issues, power failures, and numerous other factors that could prevent us from realizing the intended benefits of our manufacturing strategy and have a material adverse effect on our business.

Furthermore, compliance with cGMP requirements and other quality issues may arise during our internal efforts to scale-up manufacturing, and with our current or any future CMOs. If contaminants are discovered in our supply of our product candidates or in our manufacturing facilities or those of our CMOs, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination. We cannot assure you that any stability failures or other issues relating to the manufacture of our product candidates will not occur in the future. Additionally, we and our CMOs may experience manufacturing difficulties due to resource constraints or as a result of labor disputes or unstable political environments. If we or our CMOs were to encounter any of these difficulties, our ability to provide our product candidate to patients in clinical trials, or to provide product for treatment of patients once approved, would be jeopardized.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial resources, we intend to focus on developing product candidates for specific indications that we identify as most likely to succeed, in terms of both regulatory approval and commercialization. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that may prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

Any product candidates we develop may fail in development or be delayed to a point where they do not become commercially viable.

Before obtaining regulatory approval for the commercial distribution of any of our product candidates, we must conduct, at our own expense, extensive preclinical studies and clinical trials to demonstrate the safety and efficacy in humans of our product candidates. Preclinical and clinical testing is expensive, difficult to design and implement, can take many years to complete and is uncertain as to

outcome, and the historical failure rate for drugs in preclinical and clinical development is high. For example, in December 2019, we discontinued development of suvodirsen for patients with DMD based on the interim analysis of the Phase 1 open-label extension (OLE) study.

We, the FDA or comparable foreign regulatory authorities or an IRB, or similar foreign review board or ethics committee, may suspend clinical trials of a product candidate at any time for various reasons, including if we or they believe the healthy volunteer subjects or patients participating in such trials are being exposed to unacceptable health risks. Among other reasons, unacceptable side effects or other more serious adverse events of a product candidate in healthy volunteer subjects or patients in a clinical trial could result in the FDA or comparable foreign regulatory authorities suspending or terminating the trial and refusing to approve a particular product candidate for any or all indications of use.

Clinical trials also require the review, oversight and approval of IRBs, which review the clinical protocols for investigations that will be conducted at their institutions in order to protect the rights and welfare of human subjects. Inability to obtain or delay in obtaining IRB approval can prevent or delay the initiation and completion of clinical trials at particular sites. Furthermore, failure to provide information to the IRB as required throughout the study, such as emergent safety reports and annual updates, may result in suspension of the IRB's approval of the trial. Our product candidates may encounter problems during clinical trials that will cause us or regulatory authorities to delay, suspend or terminate these trials, or that will delay or confound the analysis of data from these trials. If we experience any such problems, we may not have the financial resources to continue development of the product candidate that is affected or any of our other product candidates. We may also lose, or be unable to enter into, collaborative arrangements for the affected product candidate and for other product candidates we are developing. The development of one or more of our product candidates can fail at any stage of testing. We may experience numerous unforeseen events during, or as a result of, preclinical studies and clinical trials that could delay or prevent regulatory approval or our ability to commercialize our product candidates, including:

- our preclinical studies or clinical trials may produce negative or inconclusive results, including results that may not meet the level of significance or clinical benefit required by the FDA or other regulators, and we may decide, or regulators may require us, to conduct additional preclinical studies or clinical trials, or we may abandon projects that we had expected to be promising;
- delays in filing clinical trial applications or comparable foreign applications or delays or failure in obtaining the necessary approvals from regulators or IRBs in order to commence a clinical trial at a prospective trial site, or their suspension or termination of a clinical trial once commenced;
- conditions imposed on us by the FDA or comparable foreign authorities regarding the scope or design of our clinical trials;
- problems in obtaining or maintaining IRB approval of trials;
- delays in enrolling patients or volunteers into clinical trials, and variability in the number and types of patients available for clinical trials;
- delays in developing and receiving regulatory approval for companion diagnostic tests to identify patients for our clinical trials;
- high drop-out rates for patients in clinical trials and substantial missing data;
- an inability to open study sites, or enroll, treat, and monitor patients due to local restrictions implemented in response to COVID-19 (emerging or future variants of COVID-19) or other global health pandemics;
- negative or inconclusive results from our clinical trials or the clinical trials of others for product candidates similar to ours;
- results from future clinical trials may not confirm positive results, if any, from earlier preclinical studies and clinical trials;
- inability to consistently manufacture, inadequate supply, or unacceptable quality of product candidate materials or other materials necessary for the conduct of our clinical trials;
- greater than anticipated clinical trial costs;
- serious and unexpected side effects that may or may not be related to the product candidate being tested that are experienced by participants in our clinical trials or by individuals using drugs similar to our product candidates;
- poor or disappointing effectiveness of our product candidates during clinical trials;
- unfavorable FDA or other regulatory agency inspection and review of a manufacturing or clinical trial site or other records relating to the clinical investigation;
- failure of our third-party contractors, investigators, or collaboration partners to comply with regulatory requirements or otherwise meet their contractual obligations in a timely manner, or at all;

- governmental or regulatory delays and changes in regulatory requirements, policy and guidelines, including the imposition of additional regulatory oversight around clinical testing generally or with respect to our product candidates in particular; or
- varying interpretations of data by the FDA and similar foreign regulatory agencies.

If we do not successfully conduct clinical development, we will not be able to market and sell products derived from our product candidates and to generate product revenues. Even if we do successfully complete clinical trials, those results are not necessarily predictive of results of additional trials that may be needed before we can submit an application for regulatory approval to the FDA or foreign regulatory agencies. If the development of any of our product candidates fails or is delayed to a point where such product candidate is no longer commercially viable, our business may be materially harmed.

Results of preclinical studies and early clinical trials may not be predictive of results of future clinical trials.

The results from preclinical studies or early clinical trials of a product candidate may not predict the results that will be obtained in subsequent subjects or in subsequent clinical trials of that product candidate or any other product candidate. The design of a clinical trial can determine whether its results will support approval of a product candidate and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. In addition, preclinical and clinical data are often susceptible to varying interpretations and analyses. Product candidates that seemingly perform satisfactorily in preclinical studies may nonetheless fail to obtain regulatory approval. For example, our preclinical studies for suvodirsen yielded positive results. However, in December 2019, the interim analysis of the Phase 1 open-label extension (OLE) study of suvodirsen for patients with DMD showed no change from baseline in dystrophin expression and resulted in our discontinuation of the suvodirsen program. There is a high failure rate for drugs proceeding through clinical trials. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in clinical development even after achieving promising results in earlier studies, and any such setbacks in our clinical development could negatively affect our business and operating results.

If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

Clinical trials of a new product candidate require the enrollment of a sufficient number of patients, including patients who are suffering from the disease the product candidate is intended to treat and who meet other eligibility criteria. Rates of patient enrollment are affected by many factors, including the COVID-19 global pandemic or emerging or future variants of COVID-19, the size of the patient population, the age and condition of the patients, the stage and severity of disease, the nature and requirements of the protocol; the proximity of patients to clinical sites, the availability of effective treatments for the relevant disease, and the eligibility criteria for the clinical trial. Delays or difficulties in patient enrollment or difficulties retaining trial participants, including as a result of the availability of existing or other investigational treatments, can result in increased costs, longer development times or termination of a clinical trial.

In addition, our success may depend, in part, on our ability to identify patients who qualify for our clinical trials, or are likely to benefit from any medicines that we may develop, which will require those potential patients to undergo a screening assay, which we also refer to as a companion diagnostic test, for the presence or absence of a particular genetic sequence. For example, in HD, we are conducting clinical trials for WVE-120101 and WVE-120102, and expect to begin dosing for WVE-003 in 2021. Each program targets a different SNP associated with the mutant alleles of the *HTT* gene, while each SNP has a particular demographic distribution and defines a subpopulation of patients suited for allele-specific interventions. Approximately 80% of the HD patient population carry one, two, or three of the three most common SNPs. We have developed a novel screening assay that is intended to identify whether a patient has the particular SNP that our product candidate is targeting, and partnered with a third party for testing in future trials. If we, or any third parties that we engage to assist us are unable to successfully identify patients with the appropriate SNPs that we are targeting, the percentage of patients with the SNPs we are targeting is lower than expected, or experience delays in testing, we may not realize the full commercial potential of any product candidates we develop.

If we are unable to successfully develop or obtain regulatory approval for companion diagnostic tests for our product candidates, or experience significant delays in doing so, our clinical trials may be delayed and our business could be materially harmed.

The development programs for some of our product candidates contemplate the development of companion diagnostic tests, which are assays or tests to identify an appropriate patient population. The success of certain of our product candidates will depend on several factors, including the successful development of, and ability to obtain regulatory approval for, companion diagnostic tests that will be used to screen and identify the right patients for our product candidates. Our goal is to develop and commercialize disease-modifying medicines for genetically defined diseases with a high degree of unmet medical need, and to become a fully integrated genetic medicines company. The target patient populations for several of our product candidates are relatively small, and it will be difficult to

successfully identify the appropriate patients for whom our product candidates are being designed without reliable, accessible, relatively inexpensive, easy-to-use companion diagnostic tests.

Companion diagnostic tests are subject to regulation by the FDA and similar regulatory authorities outside the United States as medical devices and require separate regulatory authorization prior to commercialization. We are not a medical device company, and we have limited experience developing medical devices. A more detailed description of the FDA approval process for companion diagnostic tests is included under "Business – Government Regulation – In Vitro Diagnostic Tests for Biomarkers." Given our limited experience in developing and commercializing companion diagnostic tests, we may seek to collaborate with third parties to assist us in the design, manufacture, regulatory authorization and commercialization of the companion diagnostic tests for some of our product candidates. In November 2019, we entered into a collaboration with Asuragen, Inc. ("Asuragen") for the development and commercialization of companion diagnostics for our allele-selective product candidates in HD. We, Asuragen and other potential collaborators may encounter difficulties in developing and obtaining approval for the companion diagnostic tests, including issues relating to selectivity/specificity, analytical validation, reproducibility, or clinical validation. Any delay or failure by us or our collaborators to develop or obtain regulatory authorization of the companion diagnostic tests could delay or prevent approval of our product candidates. If we, Asuragen or any other third parties that we engage to assist us, are unable to successfully develop, validate, and commercialize companion diagnostic tests for our drug candidates, or experience delays in doing so, our clinical trials and our business could be materially harmed.

We may be unable to obtain regulatory approval in the United States or foreign jurisdictions and, as a result, be unable to commercialize our product candidates and our ability to generate revenue will be materially impaired.

Our product candidates are subject to extensive governmental regulations relating to, among other things, research, testing, development, manufacturing, quality, safety, efficacy, approval, recordkeeping, reporting, labeling, storage, packaging, advertising and promotion, pricing, marketing and distribution of drugs. Rigorous preclinical studies and clinical trials and an extensive regulatory approval process are required to be successfully completed in the United States and in many foreign jurisdictions before a new drug can be marketed. Satisfaction of these and other regulatory requirements is costly, time consuming, uncertain and subject to unanticipated delays. It is possible that none of the product candidates we may develop will obtain the regulatory approvals necessary for us or our collaborators to begin selling them.

The time required to obtain FDA and other approvals is unpredictable but typically takes many years following the commencement of clinical trials, depending upon the type, complexity and novelty of the product candidate. The standards that the FDA and its foreign counterparts use when regulating companies such as ours are not always applied predictably or uniformly and can change. Any analysis we perform of data from preclinical and clinical activities is subject to confirmation and interpretation by regulatory authorities, which could delay, limit or prevent regulatory approval. We may also encounter unexpected delays or increased costs due to new government regulations, for example, from future legislation or administrative action, or from changes in FDA policy during the period of product development, clinical trials and FDA regulatory review. It is impossible to predict whether legislative changes will be enacted, or whether FDA or foreign regulations, guidance or interpretations will be changed, or what the impact of such changes, if any, may be.

Any delay or failure in obtaining required approvals could adversely affect our ability to generate revenues from the particular product candidate for which we are seeking approval. Furthermore, any regulatory approval to market a product may be subject to limitations on the approved uses for which we may market the product or the labeling or other restrictions. In addition, the FDA has the authority to require a Risk Evaluation and Mitigation Strategy ("REMS"), as a condition of approval, which may impose further requirements or restrictions on the distribution or safe use of an approved drug, such as limiting prescribing rights to certain physicians or medical centers that have undergone specialized training, limiting treatment to patients as specially defined by the indication statement or who meet certain safe-use criteria, and requiring treated patients to enroll in a registry, among other requirements. These limitations and restrictions may limit the size of the market for the product and affect reimbursement by third-party payors.

We are also subject to numerous foreign regulatory requirements governing, among other things, the conduct of clinical trials, manufacturing and marketing authorization, pricing and payment. The foreign regulatory approval process varies among countries and may include all of the risks associated with FDA approval described above, as well as risks attributable to the satisfaction of local regulations in foreign jurisdictions. Approval by the FDA does not ensure approval by comparable regulatory authorities outside of the United States and vice versa.

We have been granted orphan drug designations in the United States for some of our product candidates, but there can be no guarantee that we will maintain orphan status for these product candidates or receive approval for any product candidate with an orphan drug designation.

In 2016 and 2017, we were granted orphan drug designation under the Orphan Drug Act by the FDA for our product candidates, WVE-120101 and WVE-120102, respectively, for the treatment of HD. Subject to receiving approval from the FDA of an NDA, products granted orphan drug status are provided with seven years of marketing exclusivity in the U.S., meaning the FDA generally will not approve applications for other product candidates for the same orphan indication that contain the same active ingredient.

We are not guaranteed to maintain or receive orphan status for our current or future product candidates, and if our product candidates that were granted orphan status were to lose their status as an orphan drug or the marketing exclusivity provided to it in the United States, our business and results of operations could be materially adversely affected. While orphan status for any of our products, if granted or maintained, would provide market exclusivity in the United States for the time periods specified above, we would not be able to exclude other companies from manufacturing and/or selling products using the same active ingredient for the same indication beyond the exclusivity period applicable to our product on the basis of orphan drug status. In addition, orphan exclusivity does not block the approval of a different drug or biologic for the same rare disease or condition, nor does it block the approval of the same drug or biologic for different conditions. Even if we are the first to obtain approval of an orphan product candidate and are granted exclusivity in the United States, there are circumstances under which a later competitor product may be approved for the same indication during the period of marketing exclusivity, such as if the later product is shown to be clinically superior to our product or if we are not able to provide a sufficient quantity of the orphan drug.

Even if we obtain regulatory approvals, our marketed drugs will be subject to ongoing regulatory oversight. If we fail to comply with continuing U.S. and foreign requirements, our approvals could be limited or withdrawn, we could be subject to other penalties, and our business would be seriously harmed.

Following any initial regulatory approval of any drugs we may develop, we will also be subject to continuing regulatory oversight, including the review of adverse drug experiences and safety data that are reported after our drug products are made commercially available. This would include results from any post-marketing studies or surveillance to monitor the safety and efficacy of the drug product required as a condition of approval or agreed to by us. Any regulatory approvals that we receive for our product candidates may also be subject to limitations on the approved uses for which the product may be marketed. Other ongoing regulatory requirements include, among other things, submissions of safety and other post-marketing information and reports, registration and listing, as well as continued maintenance of our marketing application, compliance with cGMP requirements and quality oversight, compliance with post-marketing commitments, and compliance with good clinical practice for any clinical trials that we conduct post-approval. Failure to comply with these requirements could result in criminal or civil penalties, recalls, or product withdrawals. In addition, we are conducting our clinical trials and we intend to seek approval to market our product candidates in jurisdictions outside of the United States, and therefore will be subject to, and must comply with, regulatory requirements in those jurisdictions.

The FDA has significant post-market authority, including, for example, the authority to require labeling changes based on new safety information and to require post-market studies or clinical trials for a variety of reasons. The FDA also has the authority to require a REMS plan after approval, which may impose further requirements or restrictions on the distribution or use of an approved drug.

We, our CMOs, and the manufacturing facilities we use to make our product candidates will also be subject to ongoing assessment of product quality, compliance with cGMP, and periodic inspection by the FDA and potentially other regulatory agencies. The discovery of any new or previously unknown problems with us or our CMOs, or our or their manufacturing processes or facilities, including failure to maintain compliance with cGMP requirements, may result in the need for field alerts, product recalls, restrictions on the drug or manufacturer or facility, including withdrawal of the drug from the market. We may not have the ability or capacity to manufacture material at a broader commercial scale in the future. We and our CMOs currently manufacture a limited supply of clinical trial materials. Reliance on CMOs entails risks to which we would not be subject if we manufactured all of our material ourselves, including reliance on the CMO for regulatory compliance. Our product promotion and advertising will also be subject to regulatory requirements and continuing regulatory review.

If we or our collaborators, manufacturers or service providers fail to comply with applicable continuing regulatory requirements in the United States or foreign jurisdictions in which we may seek to market our products, we or they may be subject to, among other things, fines, warning letters, holds on clinical trials, refusal by the FDA or comparable foreign regulatory authorities to approve pending applications or supplements to approved applications, suspension or withdrawal of regulatory approval, product recalls and seizures, refusal to permit the import or export of products, operating restrictions, injunction, consent decree, civil penalties and criminal prosecution.

Even if we receive regulatory approval to market our product candidates, the market may not be receptive to our product candidates upon their commercial introduction, which will prevent us from becoming profitable.

Our product candidates are based upon new discoveries, technologies and therapeutic approaches. Key participants in pharmaceutical marketplaces, such as physicians, third-party payors and consumers, may not adopt a product intended to improve therapeutic results that is based on the technology employed by oligonucleotides. As a result, it may be more difficult for us to convince the medical community and third-party payors to accept and use our product, or to provide favorable reimbursement.

Other factors that we believe will materially affect market acceptance of our product candidates include:

- the timing of our receipt of any regulatory approvals, the terms of any approvals and the countries in which approvals are obtained;

- the ability to consistently manufacture our products within acceptable quality standards;
- the safety and efficacy of our product candidates, as demonstrated in clinical trials and as compared with alternative treatments, if any;
- the incidence, seriousness and severity of any side effects;
- the relative convenience and ease of administration of our product candidates;
- the willingness of patients to accept potentially new routes of administration and their risk tolerance as it relates to potentially serious side effects;
- the success of our physician education programs;
- the availability of government and third-party payer coverage and adequate reimbursement;
- the pricing of our products, particularly as compared to alternative treatments; and
- the availability of alternative effective treatments for the diseases that product candidates we develop are intended to treat and the relative risks, benefits and costs of those treatments.

In addition, our estimates regarding the potential market size may be materially different from what we currently expect at the time we commence commercialization, which could result in significant changes in our business plan and may significantly harm our results of operations and financial condition.

The pharmaceutical industry is intensely competitive. If we are unable to compete effectively with existing drugs, new treatment methods and new technologies, we may be unable to commercialize successfully any drugs that we develop.

The pharmaceutical industry is intensely competitive and rapidly changing. Many large pharmaceutical and biotechnology companies, academic institutions, governmental agencies and other public and private research organizations are pursuing the development of novel drugs for the same diseases that we are targeting or expect to target. Many of our competitors have:

- much greater financial, technical and human resources than we have at every stage of the discovery, development, manufacture and commercialization of products;
- more extensive experience in designing and conducting preclinical studies and clinical trials, obtaining regulatory approvals, and manufacturing, marketing and selling pharmaceutical products;
- product candidates that are based on previously tested or accepted technologies;
- products that have been approved or are in late stages of development; and
- collaborative arrangements in our target markets with leading companies and research institutions.

We will face intense competition from drugs that have already been approved and accepted by the medical community for the treatment of the conditions for which we may develop drugs. We also expect to face competition from new drugs that enter the market. We believe a significant number of drugs are currently under development, and may become commercially available in the future, for the treatment of conditions that our current or future product candidates are or may be designed to treat. These drugs may be more effective, safer, less expensive, or marketed and sold more effectively, than any products we develop.

Our competitors may develop or commercialize products with significant advantages over any products we are able to develop and commercialize based on many different factors, including:

- the safety and effectiveness of our products relative to alternative therapies, if any;
- the ease with which our products can be administered and the extent to which patients accept relatively new routes of administration;
- the timing and scope of regulatory approvals for these products;
- the availability and cost of manufacturing, marketing and sales capabilities;
- price;
- more extensive coverage and higher levels of reimbursement; and
- patent position.

Our competitors may therefore be more successful in commercializing their products than we are, which could adversely affect our competitive position and business. Competitive products may make any products we develop obsolete or noncompetitive before we can recover the expenses of developing and commercializing our product candidates. Such competitors could also recruit our employees, which could negatively impact our level of expertise and our ability to execute on our business plan.

If we or our collaborators, manufacturers, service providers or other third parties fail to comply with applicable healthcare laws and regulations, we or they could be subject to enforcement actions, which could affect our ability to develop, market and sell our products and may harm our reputation.

We are currently, or may in the future, be subject to federal, state, local, and comparable foreign healthcare laws and regulations relating to areas such as fraud and abuse and patients' rights. These laws may constrain the business or financial arrangements and relationships through which we conduct our operations, including how we research, market, sell and distribute our products for which we obtain marketing approval. These laws and regulations include:

- the U.S. federal Anti-Kickback Statute, which prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for a healthcare item or service, or the purchasing, recommending, or ordering of an item or service, for which payment may be made under a federal healthcare program such as Medicare or Medicaid;
- the U.S. federal false claims and civil monetary penalties laws, including the False Claims Act, which prohibits, among other things, individuals or entities from knowingly presenting or causing to be presented, claims for payment by government-funded programs such as Medicare or Medicaid that are false or fraudulent, or making a false statement to avoid, decrease, or conceal an obligation to pay money to the federal government;
- the U.S. federal Health Insurance Portability and Accountability Act ("HIPAA"), which, among other things, criminalizes a wide array of conduct involving public and private healthcare benefits, creates new civil enforcement mechanisms and increases civil and criminal penalties for healthcare fraud;
- HIPAA as amended by the Health Information Technology for Economic and Clinical Health ("HITECH") Act, and its implementing regulations, which strengthen and expand requirements relating to the privacy, security, and transmission of individually identifiable health information; and require notification to affected individuals and regulatory authorities of certain breaches of security of individually identifiable health information;
- the U.S. federal Physician Payments Sunshine Act, which requires certain manufacturers of medical devices, biological products, medical supplies, and drugs for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare and Medicaid Services ("CMS"), all transfers of value, including consulting fees, travel reimbursements, research grants, and other payments or gifts with values over $10 made to physicians and teaching hospitals, and teaching hospitals, applicable manufacturers, and applicable group purchasing organizations to report annually to CMS ownership and investment interests held by physicians and their immediate family members. Disclosure of such information is made by CMS on a publicly available website; and
- state and foreign laws comparable to each of the above federal laws, such as, for example: state anti-kickback and false claims laws applicable to commercial insurers and other non-federal payors; state laws that require pharmaceutical manufacturers to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government; state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state and foreign laws governing the privacy and security of health information, some which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

If our operations are found to be in violation of any such requirements, we may be subject to penalties, including civil or criminal penalties, criminal prosecution, monetary damages, the curtailment or restructuring of our operations, loss of eligibility to obtain approvals from the FDA, exclusion from participation in federal healthcare programs including Medicare and Medicaid, the imposition of a corporate integrity agreement with the Office of Inspector General of the Department of Health and Human Services, disgorgement, individual imprisonment, contractual damages, reputational harm, and diminished profits and future earnings, any of which could adversely affect our financial results and adversely affect our ability to operate our business. We intend to develop and implement a comprehensive corporate compliance program prior to the commercialization of our product candidates. Although effective compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, these risks cannot be entirely eliminated. Any action against us for an alleged or suspected violation could cause us to incur significant legal expenses and could divert our management's attention from the operation of our business, even if our defense is successful. In addition, achieving and sustaining compliance with applicable laws and regulations may be costly to us in terms of money, time and resources.

If we or our collaborators, manufacturers or service providers fail to comply with applicable federal, state or foreign laws or regulations, we could be subject to enforcement actions, which could affect our ability to develop, market and sell our products successfully and could harm our reputation and lead to reduced acceptance of our products by the market. These enforcement actions include, among others:

- adverse regulatory inspection findings;
- warning and/or untitled letters;
- voluntary or mandatory product recalls or public notification or medical product safety alerts to healthcare professionals;
- restrictions on, or prohibitions against, marketing our products;
- restrictions on, or prohibitions against, importation or exportation of our products;
- suspension of review or refusal to approve pending applications or supplements to approved applications;
- exclusion from participation in government-funded healthcare programs;
- exclusion from eligibility for the award of government contracts for our products;
- suspension or withdrawal of product approvals;
- product seizures;
- injunctions;
- consent decrees; and
- civil and criminal penalties, up to and including criminal prosecution resulting in fines, exclusion from healthcare reimbursement programs and imprisonment.

Moreover, federal, state or foreign laws or regulations are subject to change, and while we, our collaborators, manufacturers and/or service providers currently may be compliant, that could change due to changes in interpretation, prevailing industry standards or other reasons.

Any drugs we develop may become subject to unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, thereby harming our business.

Because our product candidates represent new approaches to the treatment of genetic-based diseases, we cannot be sure that coverage and reimbursement will be available for, or accurately estimate the potential revenue from, our product candidates or assure that coverage and reimbursement will be available for any product that we may develop. The regulations that govern marketing approvals, pricing and reimbursement for new drugs vary widely from country to country. 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. We are monitoring these regulations as several of our programs move into later stages of development; however, many of our programs are currently in the earlier stages of development and we will not be able to assess the impact of price regulations for a number of years. As a result, we might obtain regulatory approval for a product in a particular country, but then be subject to price regulations that could delay our commercial launch of the product and negatively impact any potential revenues we may be able to generate from the sale of the product in that country and potentially in other countries due to reference pricing.

Our ability to commercialize any products successfully will also depend in part on the extent to which coverage and adequate reimbursement/payment for these products and related treatments will be available from government health administration authorities, private health insurers and other organizations. Even if we succeed in bringing one or more products to the market, these products may not be considered medically necessary and/or cost-effective, and the amount reimbursed for any products may be insufficient to allow us to sell our products on a competitive basis. At this time, we are unable to determine their cost effectiveness or the likely level or method of reimbursement for our product candidates. Increasingly, third-party payors, such as government and private insurance plans, are requiring that drug companies provide them with predetermined discounts from list prices, and are seeking to reduce the prices charged or the amounts paid for pharmaceutical products. If the price we are able to charge for any products we develop, or the payments provided for such products, is inadequate in light of our development and other costs, our return on investment could be adversely affected.

We currently expect that any drugs we develop may need to be administered under the supervision of a physician on an outpatient basis. Under currently applicable U.S. law, certain drugs that are not usually self-administered (such as most injectable drugs) may be eligible for coverage under the Medicare Part B program if:

- they are incident to a physician's services;
- they are reasonable and necessary for the diagnosis or treatment of the illness or injury for which they are administered according to accepted standards of medical practice; and
- they have been approved by the FDA and meet other requirements of the statute.

There may be significant delays in obtaining coverage for newly-approved drugs, and coverage may be more limited than the indications for which the drug is approved by the FDA or comparable foreign regulatory authorities. Patients who are prescribed medications for the treatment of their conditions, and their prescribing physicians, generally rely on third-party payors to pay all or part of the costs associated with their prescription drugs. Patients are unlikely to use our products unless coverage is provided and payment is adequate to cover all or a significant portion of the cost of our products. Therefore, coverage and adequate payment is critical to new product acceptance. Coverage decisions may depend upon clinical and economic standards that disfavor new drug products when more established or lower cost therapeutic alternatives are already available or subsequently become available. Moreover, eligibility for coverage 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 payments for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement may be based on payments allowed for lower-cost drugs that are already reimbursed, may be incorporated into existing payments for other services and may reflect budgetary constraints or imperfections in Medicare data. 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 rates. However, no uniform policy requirement for coverage and reimbursement for drug products exists among third-party payors in the United States. Therefore, coverage and reimbursement for drug products can differ significantly from payor to payor. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. Our inability to promptly obtain coverage and adequate reimbursement rates from both government-funded and private payors for new drugs that we develop and for which we obtain regulatory approval could adversely affect our operating results, our ability to raise capital needed to commercialize products, and our overall financial condition.

We believe that the efforts of governments and third-party payors to contain or reduce the cost of healthcare and legislative and regulatory proposals to broaden the availability of healthcare will continue to affect the business and financial condition of pharmaceutical and biopharmaceutical companies. A number of legislative and regulatory changes in the healthcare system in the United States and other major healthcare markets have been proposed and/or adopted in recent years, and such efforts have expanded substantially in recent years. These developments have included prescription drug benefit legislation that was enacted in 2003 and took effect in January 2006, healthcare reform legislation enacted by certain states, and major healthcare reform legislation that was passed by Congress and enacted into law in the United States in 2010. These developments could, directly or indirectly, affect our ability to sell our products, if approved, at a favorable price.

In particular, in March 2010, the Patient Protection and Affordable Care Act (the "ACA") was signed into law. This legislation changed the system of healthcare insurance and benefits and was intended to broaden access to healthcare coverage, enhance remedies against fraud and abuse, add transparency requirements for the healthcare and health insurance industries, impose taxes and fees on the healthcare industry, impose health policy reforms, and control costs. This law also contains provisions that would affect companies in the pharmaceutical industry and other healthcare related industries by imposing additional costs and changes to business practices. Since its enactment, there have been judicial and Congressional challenges to certain aspects of the ACA. The uncertainty around the future of the ACA, and in particular the impact to reimbursement levels, may lead to uncertainty or delay in the purchasing decisions of our customers, which may in turn negatively impact our product sales. We continue to evaluate the effect that the ACA has or any potential changes to the ACA could have on our business. Additional federal and state legislative and regulatory developments are likely, and we expect ongoing initiatives in the United States to increase pressure on drug pricing and reimbursement. Such reforms could have an adverse effect on anticipated revenues from product candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our overall financial condition and ability to develop product candidates.

Our ability to obtain services, reimbursement or funding from the federal government may be impacted by possible reductions in federal spending.

Other legislative changes have been proposed and adopted since the ACA was enacted. For example, in August 2011, President Obama signed into law the Budget Control Act of 2011, which, among other things, created the Joint Select Committee on Deficit Reduction (Joint Select Committee) to recommend to Congress proposals in spending reductions. The failure of Congress to enact deficit reduction measures of at least $1.2 trillion for the years 2013 through 2021 triggered the legislation's automatic reduction to several government programs. These cuts included aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect beginning on April 1, 2013, and will stay in effect through 2024 unless additional Congressional action is taken. Additionally, under the American Taxpayer Relief Act of 2012, which was enacted on January 1, 2013, the imposition of these automatic cuts was delayed until March 1, 2013. As required by law, President Obama issued a sequestration order on March 1, 2013. Certain of these automatic cuts have been implemented resulting in reductions in Medicare payments to physicians, hospitals, and other healthcare providers, among other things. The full impact on our business of these automatic cuts is uncertain.

If other federal spending is reduced, any budgetary shortfalls may also impact the ability of relevant agencies, such as the FDA or National Institutes of Health to continue to function. Amounts allocated to federal grants and contracts may be reduced or eliminated. These reductions may also impact the ability of relevant agencies to timely review and approve drug research and development, manufacturing, and marketing activities, which may delay our ability to develop, market and sell any products we may develop.

Changes in laws and regulations affecting the healthcare industry could adversely affect our business.

All aspects of our business, including research and development, manufacturing, marketing, pricing, sales, litigation, and intellectual property rights, are subject to extensive legislation and regulation. Changes in applicable U.S. federal and state laws and agency regulation, as well as foreign laws and regulations, could have a materially negative impact on our business. In the United States and in some other jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of our product candidates or any potential future product candidates of ours, restrict or regulate post-approval activities, or affect our ability to profitably sell any product candidates for which we obtain marketing approval. 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. Congress also must reauthorize the FDA's user fee programs every five years and often makes changes to those programs in addition to policy or procedural changes that may be negotiated between the FDA and industry stakeholders as part of this periodic reauthorization process. The negotiation process for the next cycle of prescription drug and medical device user fee programs is beginning in 2020 as those programs must be reauthorized by Congress in mid-2022.

Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in health care systems with the stated goals of containing health care costs, improving quality and/or expanding access. In the United States, the pharmaceutical industry has been a focus of these efforts and has been significantly affected by major legislative initiatives. In March 2010, Congress passed the ACA, which substantially changed the way health care is financed by both the government and private insurers, and significantly impacts the United States pharmaceutical industry. As another example, the 2021 Consolidated Appropriations Act signed into law on December 27, 2020 incorporated extensive health care provisions and amendments to existing laws, including a requirement that all manufacturers of drug products covered under Medicare Part B report the product's average sales price, or ASP, to DHHS beginning on January 1, 2022, subject to enforcement via civil money penalties.

There remain judicial and Congressional challenges to certain aspects of the ACA, and as a result certain sections of the ACA have not been fully implemented or effectively repealed. In particular, in December of 2018, a Texas U.S. District Court Judge ruled that the ACA is unconstitutional in its entirety because the individual mandate was repealed by Congress as part of the Tax Cuts and Jobs Act, effective January 1, 2019. In December 2019, the Fifth Circuit Court of Appeals upheld the district court's ruling that the individual mandate in the ACA was unconstitutional but remanded the case to the district court to determine whether other reforms enacted as part of the ACA but not specifically related to the individual mandate or health insurance could be severed from the rest of the ACA so as not to have the law declared invalid in its entirety. On March 2, 2020, the United States Supreme Court granted the petitions for writs of certiorari to review this case and allocated one hour for oral arguments, which occurred on November 10, 2020. A decision from the Supreme Court is expected to be issued in spring 2021. It is unclear how this litigation and other efforts to repeal and replace the ACA will affect the implementation of that law, the pharmaceutical industry more generally, and our business. Additionally, the 2020 federal spending package permanently eliminated, effective January 1, 2020, the ACA-mandated "Cadillac" tax on high-cost employer-sponsored health coverage and medical device tax and, effective January 1, 2021, also eliminates the health insurer tax. Further, the Bipartisan Budget Act of 2018, among other things, amended the ACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." In addition, CMS published a final rule that would give states greater flexibility, effective January 1, 2020, in setting benchmarks for insurers in the individual and small group

marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. We continue to evaluate the potential impact of the ACA and its possible repeal or replacement on our business.

The uncertainty around the future of the ACA, and in particular the impact to reimbursement levels, may lead to uncertainty or delay in the purchasing decisions of our customers, which may in turn negatively impact our product sales. If there are not adequate reimbursement levels, our business and results of operations could be adversely affected.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. These changes include aggregate reductions to Medicare payments to providers of up to 2% per fiscal year pursuant to the Budget Control Act of 2011, which began in 2013 and will remain in effect through 2030 unless additional Congressional action is taken. However, the Medicare sequester reductions under the Budget Control Act of 2011 was suspended from May 1, 2020 through December 31, 2020 due to the COVID-19 pandemic, pursuant to provisions of the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act, which also extended the sequester by one year, through 2030, in order to offset the added expense of the 2020 cancellation. The 2021 Consolidated Appropriations Act was subsequently signed into law on December 27, 2020 and extends the CARES Act suspension period to March 31, 2021.

In addition, the Drug Supply Chain Security Act enacted in 2013 imposed obligations on manufacturers of pharmaceutical products related to product tracking and tracing. More recently, on December 20, 2019, President Trump signed the Further Consolidated Appropriations Act for 2020 into law (P.L. 116-94) that includes a piece of bipartisan legislation called the CREATES Act. The CREATES Act aims to address the concern articulated by both the FDA and others in the industry that some brand manufacturers have improperly restricted the distribution of their products, including by invoking the existence of a REMS for certain products, to deny generic and biosimilar product developers access to samples of brand products. The CREATES Act establishes a private cause of action that permits a generic or biosimilar product developer to sue the brand manufacturer to compel it to furnish the necessary samples on “commercially reasonable, market-based terms.” Whether and how generic and biosimilar product developments will use this new pathway, as well as the likely outcome of any legal challenges to provisions of the CREATES Act, remain highly uncertain and its potential effects on our future commercial products are unknown. Other legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We are unsure whether additional legislative changes will be enacted, or whether the current regulations, guidance or interpretations will be changed, or whether such changes will have any impact on our business.

Additionally, there has been heightened governmental scrutiny in the United States of pharmaceutical pricing practices considering the rising cost of prescription drugs and biologics. Such scrutiny has resulted in several recent congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. For example, state legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In December 2020, the U.S. Supreme Court held unanimously that federal law does not preempt the states’ ability to regulate pharmaceutical benefit managers (PBMs) and other members of the health care and pharmaceutical supply chain, an important decision that may lead to further and more aggressive efforts by states in this area.

At the federal level, DHHS has solicited feedback on various measures intended to lower drug prices and reduce the out of pocket costs of drugs and has implemented others under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage plans the option to use step therapy for Part B drugs beginning January 1, 2020. This final rule codified CMS’s policy change that was effective January 1, 2019. In addition, in September 2020, the FDA finalized a rulemaking to establish a system whereby state governmental entities could lawfully import and distribute prescription drugs sourced from Canada. Those new regulations became effective on November 30, 2020, although the impact of such future programs is uncertain in part because lawsuits have been filed challenging the government’s authority to promulgate them. The final regulations may also be vulnerable to being overturned by a joint resolution of disapproval from Congress under the procedures set forth in the Congressional Review Act, which could be applied to regulatory actions taken by the Trump administration on or after August 21, 2020 (i.e., in the last 60 days of legislative session of the 116th Congress). Congress and the executive branch have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. For example, in July 2020, President Trump announced four executive orders related to prescription drug pricing that attempted to implement several of his Administration’s proposals, including a policy that would tie Medicare Part B drug prices to international drug prices; one that directed DHHS to finalize the Canadian drug importation proposed rule previously issued by DHHS (which has since been finalized, as noted above) and made other changes allowing for personal importation of drugs from Canada; one that directed DHHS to finalize the rulemaking process on modifying the anti-kickback law safe harbors for plans, pharmacies, and pharmaceutical benefit managers after DHHS confirms that the action is not projected to increase federal spending, Medicare beneficiary premiums, or patients’ total out-of-pocket costs (which DHHS finalized

in November 2020, also making those rules subject to potentially being overturned under the Congressional Review Act); and one that reduces costs of insulin and epinephrine auto-injectors to patients of federally qualified health centers. President Trump also issued another executive order on September 13, 2020 that directed DHHS to undertake rulemaking in order to test an international reference pricing model for prescription drug products, which was also implemented by DHHS and then challenged in federal court by industry groups in December 2020. The probability of success of these newly announced policies and their impact on the U.S. prescription drug marketplace is unknown. There are likely to be continued political and legal challenges associated with implementing these reforms as they are currently envisioned, and the January 20, 2021 transition to a new Democrat-led presidential administration created further uncertainty. Following his inauguration, President Biden took immediate steps to order a regulatory freeze on all pending substantive executive actions in order to permit incoming department and agency heads to review whether questions of fact, policy, and law may be implicated and to determine how to proceed. The implementation of cost containment measures or other health care reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our products. Current and future health care legislation could have a significant impact on our business. There is uncertainty with respect to the impact these changes, if any, may have, and any changes likely will take time to unfold. In addition, it is possible that additional governmental action is taken to address the COVID-19 pandemic. For example, on April 18, 2020, CMS announced that qualified health plan issuers under the ACA may suspend activities related to the collection and reporting of quality data that would have otherwise been reported between May and June 2020 given the challenges health care providers are facing responding to the COVID-19 virus. Any additional federal or state health care reform measures could limit the amounts that third-party payers will pay for health care products and services, and, in turn, could significantly reduce the projected value of certain development projects and reduce our profitability.

Risks associated with our operations outside of the United States and developments in international trade by the U.S. and foreign governments could adversely affect our business.

We have operations and conduct business outside the United States, and we plan to continue to expand these operations. Therefore, we are subject to risks related to operating in foreign countries, which include unfamiliar foreign laws or regulatory requirements or unexpected changes to those laws or requirements; other laws and regulatory requirements to which our business activities abroad are subject, such as the Foreign Corrupt Practices Act and the U.K. Bribery Act; changes in the political or economic condition of a specific country or region; fluctuations in the value of foreign currency versus the U.S. dollar; our ability to deploy overseas funds in an efficient manner; tariffs, trade protection measures, import or export licensing requirements, trade embargoes, and sanctions (including those administered by the Office of Foreign Assets Control of the U.S. Department of the Treasury), and other trade barriers; global instability from an outbreak of pandemic or contagious disease, including the COVID-19 global pandemic and variants thereof; difficulties in attracting and retaining qualified personnel; and cultural differences in the conduct of business. For example, given developments related to international trade over the past few years, unexpected changes in tariffs could adversely affect our cost of goods sold and/or the foreign sales of our product candidates. Further complicating potential uncertainties caused by conducting business outside the United States are recent political movements that are changing decades-old institutions, including, for example, in 2016, the United Kingdom held a referendum in which voters approved an exit from the European Union, commonly referred to as “Brexit.” On March 29, 2017, the United Kingdom formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. The withdrawal of the United Kingdom from the European Union took effect on January 31, 2020, the effective date of the withdrawal agreement, with a transition period that ended on December 31, 2020. Since a significant proportion of the regulatory framework in the United Kingdom was, prior to Brexit, derived from European Union directives and regulations, Brexit and the new Trade and Cooperation Agreement between the European Union and the United Kingdom that took provisional effect on January 1, 2021 could materially impact the regulatory regime with respect to the approval of any product candidates in the United Kingdom. Changes impacting our ability to conduct business in the United Kingdom or other European Union countries, or changes to the regulatory regime applicable to our operations in those countries (such as with respect to the approval of our product candidates), may materially and adversely impact our business, prospects, operating results, and financial condition. Given the lack of comparable precedent, it is unclear what financial, trade, regulatory and legal implications the withdrawal of the United Kingdom from the European Union would have and how such withdrawal would affect us. Any of these effects of Brexit, among others, could adversely affect our business, financial condition and operating results.

We or third parties upon whom we depend may be adversely affected by natural disasters and/or health epidemics (including the COVID-19 pandemic and variants thereof), and our business, financial condition and results of operations could be adversely affected.

Natural disasters could severely disrupt our operations and have a material adverse effect on our business operations. If a natural disaster, health epidemic, or other event beyond our control occurred that prevented us from using all or a significant portion of our office, manufacturing and/or lab spaces, that damaged critical infrastructure, such as the manufacturing facilities of our third-party contract manufacturers, or that otherwise disrupted operations, it may be difficult for us to continue our business for a substantial period of time. Any outbreak of contagious diseases, or other adverse public health developments, could have a material and adverse effect on our business operations. For example, COVID-19 was declared a pandemic by the World Health Organization on March 11, 2020 and is continuing to evolve. The COVID-19 global pandemic, including emerging or future variants of COVID-19, and its

impact on our business is highly uncertain and subject to change. We do not yet know the full extent of potential delays or long-term impacts on our business, our preclinical studies and clinical trials, healthcare systems or the global economy. In addition, certain of our research and development efforts are conducted globally. A health epidemic or other outbreak could materially and adversely affect our business, financial condition and results of operations.

The disaster recovery and business continuity plans we have in place may prove inadequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which could have a material adverse effect on our business.

There is a substantial risk of product liability claims in our business. If we are unable to obtain or maintain sufficient insurance, a product liability claim against us could adversely affect our business.

Our business exposes us to significant potential product liability risks that are inherent in the development, testing, manufacturing and marketing of human therapeutic products. Product liability claims could delay or prevent completion of our clinical development programs. In addition, if any of our collaboration partners face product liability claims, our programs could also be affected and our business could be harmed. If we succeed in marketing products, such claims could result in an FDA investigation of the safety and effectiveness of our products, our manufacturing processes and facilities or our marketing programs, and potentially a recall of our products or more serious enforcement action, limitations on the approved indications for which they may be used, or suspension or withdrawal of approvals. Regardless of the merits or eventual outcome, liability claims may also result in decreased demand for our products, injury to our reputation, costs to defend the related litigation, a diversion of management's time and our resources, substantial monetary awards to trial participants or patients and a decline in our share price. Any insurance we obtain may not provide sufficient coverage against potential liabilities. Furthermore, clinical trial and product liability insurance is becoming increasingly expensive. As a result, we may be unable to obtain or maintain sufficient insurance at a reasonable cost to protect us against losses caused by product liability claims that could adversely affect our business.

If we do not comply with laws regulating the protection of the environment and health and human safety, our business could be adversely affected.

Our research, development and manufacturing processes involve the use of hazardous materials, chemicals and various radioactive compounds. We maintain quantities of various flammable and toxic chemicals in our facilities that are required for our research, development and manufacturing activities. We are subject to federal, state and local laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. We believe our procedures for storing, handling and disposing of these materials comply with the relevant guidelines and laws of the jurisdictions in which our facilities are located. Although we believe that our safety procedures for handling and disposing of these materials comply with the standards mandated by applicable regulations, the risk of accidental contamination or injury from these materials cannot be eliminated. If an accident occurs, we could be held liable for resulting damages, which could be substantial. We are also subject to numerous environmental, health and workplace safety laws and regulations, including those governing laboratory procedures, exposure to blood-borne pathogens and the handling of biohazardous materials. 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 these materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials. Additional federal, state and local laws and regulations affecting our operations may be adopted in the future. We may incur substantial costs to comply with, and substantial fines or penalties if we violate any of, these laws or regulations.

Risks Related to Our Dependence on Third Parties

We depend on collaborations with third parties for the development and commercialization of certain of our product candidates.

We depend on third-party collaborators for the co-development and co-commercialization of certain of our product candidates and we face significant competition to the extent we elect to collaborate with others. Our potential future collaborators include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators. In April 2018, we commenced a collaboration with Takeda to discover, develop and commercialize oligonucleotides for disorders of the CNS. The collaboration provides Takeda with the option to globally co-develop and commercialize programs targeting HD, ALS, FTD, and SCA3, which we will have the right to co-commercialize in the United States. In addition, Takeda will have the right to exclusively license multiple preclinical programs for CNS disorders, including Alzheimer's disease ("AD") and Parkinson's disease ("PD"). Collaborations are complex and time-consuming to negotiate and document. We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. We may also be restricted under existing license or collaboration agreements from entering into agreements on certain terms with other potential collaborators. If we are unable to enter into collaborations with respect to a product candidate, we may have to curtail the development of such product

candidate, 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 our product candidates or bring them to market and generate product revenue.

Depending on the type of collaborations we enter into, we may have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on our collaborators' abilities and efforts to successfully perform the functions assigned to them in these arrangements.

Collaborations involving our product candidates may pose the following risks to us:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not pursue development and commercialization of our product candidates 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 products or product candidates 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;
- a collaborator with marketing and distribution rights to one or more products may not commit sufficient resources to the marketing and distribution of such product or products;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our proprietary information or expose us to potential litigation;
- disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of our products or product candidates or that result in costly litigation or arbitration that diverts management attention and resources; and
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner, or at all. Further, if a present or future collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program could be delayed, diminished or terminated.

We may not be able to execute our business strategy optimally if we are unable to maintain our existing collaborations or enter into new collaborations with partners that can provide sales, marketing and distribution capabilities and funds for the development and commercialization of our product candidates.

We do not currently have any sales and marketing or distribution capabilities. Accordingly, we have entered into a collaboration with Takeda in CNS, which we believe can assist us in building these capabilities. We may also enter into additional alliances in the future. We have selectively chosen to enter into a collaboration in the field of CNS with Takeda because we believe this is the optimal way for us to leverage our resources and create significant value for ourselves and our shareholders, as we advance oligonucleotide candidates for genetically defined diseases.

Depending on the collaborations that we enter into, we may expect our collaborators to provide assistance with development, regulatory affairs, marketing, sales and distribution, among other areas. Our future revenues may depend heavily on the success of the efforts of these third parties. For example, under our collaboration with Takeda, if Takeda exercises its option with respect to any of our programs in HD, ALS, FTD or SCA3, we will rely on Takeda for commercialization of such optioned programs outside of the United States. In addition, Takeda will be solely responsible for the potential commercialization of additional to-be-identified preclinical CNS programs globally based on targets that Takeda identifies.

We may not be successful in our collaborations due to various factors, including our ability to successfully demonstrate proof of mechanism in humans, our ability to demonstrate the safety and efficacy of our specific product candidates, our ability to manufacture or have third parties manufacture our product candidates, the strength of our intellectual property and/or concerns about potential challenges to or limitations of our intellectual property. To the extent we have entered into, or enter into new, collaborations, we may not be able to maintain them if, for example, development or approval of a product candidate is delayed, challenges are raised as to the validity or scope of our intellectual property or sales of an approved drug are lower than we or our collaboration partner expected.

For certain product candidates that we may develop, we have formed collaborations to fund all or part of the costs of drug development and commercialization, such as our collaboration with Takeda. We may not, however, be able to enter into additional collaborations for certain other programs, and the terms of any collaboration agreement we do secure may not be favorable to us. If we are not successful in our efforts to enter into future collaboration arrangements with respect to one or more of our product candidates, we may not have sufficient funds to develop that or any other product candidate internally, or to bring any product candidates to market. If we do not have sufficient funds to develop and bring our product candidates to market, we will not be able to generate sales revenues from these product candidates, and this will substantially harm our business.

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

We do not independently conduct all aspects of our drug discovery activities, compound formulation research, preclinical studies, or clinical trials of product candidates. We currently rely, and expect to continue to rely, on third parties to conduct some aspects of our research and development, preclinical and clinical studies. Any of these third parties may terminate their engagements with us at any time. 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 will reduce our control over these activities but will not relieve us of our responsibilities. For example, for product candidates that we develop and commercialize on our own, we will remain responsible for ensuring that each of our studies that support our clinical trial applications and our clinical trials are conducted in accordance with the study plan and protocols for the trial. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our studies in accordance with regulatory requirements or our stated study plans and protocols, we will not be able to complete, or may be delayed in completing, the necessary preclinical studies to enable us or our strategic alliance partners to select viable product candidates for clinical trial application submissions and will not be able to, or may be delayed in our efforts to, successfully develop and commercialize such product candidates.

We rely on third parties to design, conduct, supervise and monitor our preclinical studies and clinical trials, and if those third parties perform in an unsatisfactory manner, it may harm our business.

We rely on third party clinical investigators, contract research organizations (“CROs”), clinical data management organizations and consultants to design, conduct, supervise and monitor preclinical studies and clinical trials of our product candidates. Because we rely on third parties and do not have the ability to conduct preclinical studies or clinical trials independently, we have less control over the timing, quality and other aspects of preclinical studies and clinical trials than we would if we conducted them on our own. These investigators, CROs and consultants are not our employees and we have limited control over the amount of time and resources that they dedicate to our programs. These third parties may have contractual relationships with other entities, some of which may be our competitors, which may draw time and resources from our programs. Further, these third parties may not be diligent, careful or timely in conducting our preclinical studies or clinical trials, resulting in the preclinical studies or clinical trials being delayed or unsuccessful.

If we cannot contract with acceptable third parties on commercially reasonable terms, or at all, or if these third parties do not carry out their contractual duties, satisfy legal and regulatory requirements for the conduct of preclinical studies or clinical trials or meet expected deadlines, our preclinical and clinical development programs could be delayed and otherwise adversely affected. In all events, we are responsible for ensuring that each of our preclinical studies and clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. The FDA and other health authorities require clinical trials to be conducted in accordance with good clinical practices, including conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical trial participants are protected. If we or our CROs fail to comply with these requirements, the data generated in our clinical trials may be deemed unreliable or

uninterpretable and the FDA and other health authorities may require us to perform additional clinical trials. Our reliance on third parties that we do not control does not relieve us of these responsibilities and requirements. Any such event could adversely affect our business, financial condition, results of operations and prospects.

We rely on third parties in the supply and manufacture our product candidates for our research, preclinical and clinical activities, and may do the same for commercial supplies of our product candidates.

While we have built our own internal manufacturing capabilities, we have not yet manufactured our product candidates on a commercial scale, and may not be able to do so for any of our product candidates. In addition, we currently rely on third parties in the supply and manufacture the materials for our research, preclinical and clinical activities and may continue to do so for the foreseeable future. We may do the same for the commercial supply of our drug product. We use third parties to perform additional steps in the manufacturing process, such as the filling, finishing and labeling of vials and storage of our product candidates and we expect to do so for the foreseeable future. There can be no assurance that our supply of research and development, preclinical and clinical development drug candidates and other materials will not be limited, interrupted or restricted or will be of satisfactory quality or continue to be available at acceptable prices. Replacement of any of the third parties we may engage could require significant effort and expertise because there may be a limited number of qualified replacements. In addition, raw materials, reagents, and components used in the manufacturing process, particularly those for which we have no other source or supplier, may not be available, may not be suitable or acceptable for use due to material or component defects, or may introduce variability into the supply of our product candidates. Furthermore, with the increase of companies developing nucleic acid therapeutics, there may be increased competition for the supply of the raw materials that are necessary to make our oligonucleotides, which could severely impact the manufacturing of our product candidates.

We may be unable to identify manufacturers on acceptable terms or at all because the number of potential manufacturers is limited and they must be acceptable to the FDA or approved by foreign regulatory authorities Suppliers and manufacturers, including us, must meet applicable manufacturing requirements, including compliance with cGMP regulations, and undergo rigorous facility and process validation tests required by regulatory authorities in order to comply with regulatory standards. In the event that any of our suppliers or manufacturers fail to comply with such requirements or to perform its obligations to us in relation to quality, timing or otherwise, some of which may be out of their or our control, or if our supply of components or other materials becomes limited or interrupted for other reasons, we may be forced to increase the manufacturing of the materials ourselves, for which we currently have limited capabilities and resources, or enter into an agreement with another third party, which we may not be able to do on reasonable terms, if at all. Any interruption of the development or operation of the manufacturing of our product candidates, such as order delays for equipment or materials, equipment malfunction, quality control and quality assurance issues, regulatory delays and possible negative effects of such delays on supply chains and expected timelines for product availability, production yield issues, shortages of qualified personnel, discontinuation of a facility or business or failure or damage to a facility resulting from natural disasters, could result in the cancellation of shipments, loss of product in the manufacturing process or a shortfall in available product candidates or materials. In some cases, the technical skills or technology required to manufacture our product candidates may be unique or proprietary to the original manufacturer and we may have difficulty, or there may be contractual restrictions prohibiting us from, transferring such skills or technology to another third party and a feasible alternative may not exist. These factors would increase our reliance on such manufacturer or require us to obtain a license from such manufacturer in order to have another third party manufacture our product candidates. If we are required to change manufacturers for any reason, we will be required to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. The delays associated with the verification of a new manufacturer could negatively affect our ability to develop product candidates in a timely manner or within budget.

We may rely on third party manufacturers if we receive regulatory approval for any product candidate. To the extent that we have existing, or enter into future, manufacturing arrangements with third parties, we will depend on these third parties to perform their obligations in a timely manner consistent with contractual and regulatory requirements, including those related to quality control and assurance. We may also be required to enter into long-term manufacturing agreements that contain exclusivity provisions and/or substantial termination penalties which could have a material adverse effect on our business prior to or after commercialization of any of our product candidates. If we are unable to obtain or maintain third-party manufacturing for product candidates, or to do so on commercially reasonable terms, we may not be able to develop and commercialize our product candidates successfully. Failure to execute on our manufacturing requirements, either by us or by one of our third-party vendors, could adversely affect our business in a number of ways, including:

- an inability to initiate or continue clinical trials of product candidates under development;
- delays in submitting regulatory applications, or receiving regulatory approvals, for product candidates;
- loss of the cooperation of a collaborator;
- additional inspections by regulatory authorities;
- requirements to cease distribution or to recall batches of our product candidates; and
- in the event of approval to market and commercialize a product candidate, an inability to meet commercial demands for our products.

If any of our product candidates are approved for marketing and commercialization and we are unable to develop sales, marketing and distribution capabilities on our own, or enter into agreements with third parties to perform these functions on acceptable terms, we will be unable to commercialize successfully any such future products.

We currently have no sales, marketing or distribution capabilities. In addition, while our collaboration with Takeda will provide us with know-how and experience related to commercialization, we have limited experience of our own. If any of our product candidates is approved, we will need to develop internal sales, marketing and distribution capabilities to commercialize such products, which would be expensive and time-consuming, or rely on or enter into additional collaborations with third parties to perform these services. If we decide to market our products directly, we will need to commit significant financial and managerial resources to develop a marketing and sales force with technical expertise and supporting distribution, administration and compliance capabilities. If we rely on third parties with such capabilities to market our products or decide to co-promote products with collaborators, we will need to establish and maintain marketing and distribution arrangements with third parties, and there can be no assurance that we will be able to enter into such arrangements on acceptable terms or at all. In entering into third-party marketing or distribution arrangements, any revenue we may receive will depend upon the efforts of the third parties and there can be no assurance that such third parties will establish adequate sales and distribution capabilities or be successful in gaining market acceptance of any approved product. If we are not successful in commercializing any product approved in the future, either on our own or through third parties, our business, financial condition, results of operations and prospects would be adversely affected.

Risks Related to Managing Our Operations

If we are unable to attract and retain qualified key management and scientists, staff, consultants and advisors, our ability to implement our business plan may be adversely affected.

We are highly dependent upon our senior management and our scientific, clinical and medical staff and advisors. The loss of the service of any of the members of our senior management or other key employees could delay our research and development programs and materially harm our business, financial condition, results of operations and prospects. In addition, we expect that we will continue to have an increased need to recruit and hire qualified personnel as we advance our programs and expand operations. Failure to successfully recruit and retain personnel could impact our anticipated development plans and timelines. For example, in 2019, as a result of the stock price decline and our workforce reduction following the announcement of our decision to discontinue our development of suvodirsen in DMD, and more recently, in light of the COVID-19 global pandemic, we may face challenges in retaining and attracting employees to support our research and development efforts, and our failure to do so could have an adverse effect on our ability to execute on our business plan. We are dependent on the continued service of our technical personnel because of the highly technical and novel nature of our product candidates, platform and technologies and the specialized nature of the regulatory approval process. Replacing such personnel may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully execute our business strategy. Because our management team and key employees are not obligated to provide us with continued service, they could terminate their employment with us at any time without penalty. We do not maintain key person life insurance policies on any of our management team members or key employees. Our future success will depend in large part on our continued ability to attract and retain highly qualified scientific, technical and management personnel, as well as personnel with expertise in preclinical and clinical testing, manufacturing, governmental regulation and commercialization. We face competition for personnel from other companies, universities, public and private research institutions, government entities and other organizations. If we are unable to attract and retain qualified personnel, the rate and success at which we may be able to discover and develop our product candidates and implement our business plan will be limited.

As we continue our preclinical studies and clinical trials and advance to further clinical development, we may experience difficulties in managing our growth and expanding our operations.

Although we have assembled a team of employees with experience developing medicines and obtaining regulatory approval to market those medicines, we have limited experience as a company in drug development. We are conducting clinical trials of our two most advanced programs in HD and expect to deliver data from those trials at the end of the first quarter of 2021. Also in 2021, we expect to initiate dosing in three new clinical trials with compounds containing our novel PN backbone chemistry modifications, including WVE-003 in HD, WVE-004 in ALS and FTD, and WVE-N531 in DMD. Beyond neurology, we are advancing our first ADAR editing program in alpha-1 antitrypsin disorders. We are also evaluating our ophthalmology programs and continue to explore additional targets in neurology and hepatic disorders. As we advance product candidates through preclinical studies and clinical trials, we will need to expand our development, regulatory and manufacturing capabilities or contract with other organizations to provide these capabilities for us. In addition, we must manage our relationships with collaborators or partners, suppliers and other organizations, including our collaboration with Takeda. Our ability to manage our operations and future growth will require us to continue to improve our operational, financial and management controls, reporting systems and procedures. We may not be able to implement improvements to our management information and control systems in an efficient or timely manner and may discover deficiencies in existing systems and controls. In addition, our future growth may require significant capital expenditures and may divert financial resources from other projects, such as the development of our product candidates. If we are unable to effectively manage our future growth, our expenses may increase and our ability to generate revenue could be reduced.

Our employees, consultants and collaborators may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements.

We are exposed to the risk of fraud and other misconduct by our employees, consultants and collaborators. Such misconduct could include intentional failures to comply with FDA and other foreign agency regulations, provide accurate information to the FDA, comply with manufacturing standards required by the FDA or that we may establish, comply with federal and state healthcare fraud and abuse laws and regulations, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter such misconduct, 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 or 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 significant fines or other sanctions.

Security breaches, loss of data and other disruptions could compromise sensitive information related to our business, prevent us from accessing critical information or expose us to liability, which could adversely affect our business and our reputation.

In the ordinary course of our business, we, our CROs and other third parties on which we rely collect and store sensitive data, including legally protected patient health information, personally identifiable information about our employees, intellectual property, and proprietary business information. We manage and maintain our applications and data utilizing on-site systems. These applications and data encompass a wide variety of business-critical information, including research and development information and business and financial information.

The secure processing, storage, maintenance and transmission of this critical information by us, or our CROs and other third parties, is vital to our operations and business strategy. Although we are proactive in our approach and take measures to protect sensitive information from unauthorized access or disclosure, our information technology and infrastructure, or that of our CROs or other third parties, may be vulnerable to attacks by hackers, viruses, breaches, interruptions due to employee error, malfeasance or other disruptions, lapses in compliance with privacy and security mandates, or damage from natural disasters, terrorism, war and telecommunication and electrical failures. Any such event could compromise our networks, or that of our CROs or other third parties, and the information stored there could be accessed by unauthorized parties, publicly disclosed, lost or stolen.

We have measures in place that are designed to detect and respond to such security incidents and breaches of privacy and security mandates. Any such access, disclosure or other loss of information could result in legal claims or proceedings, liability under laws that protect the privacy of personal information, such as the HIPAA, government enforcement actions and regulatory penalties. Unauthorized access, loss or dissemination could also disrupt our operations, including our ability to conduct research and development activities, process and prepare company financial information, manage various general and administrative aspects of our business and damage our reputation, any of which could adversely affect our business. For example, the loss of clinical trial data from completed or ongoing or planned clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. In addition, there can be no assurance that we, or our CROs and other third parties, will promptly detect any such disruption or security breach, if at all. To the extent that any disruption or security breach were to result in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development of our product candidates could be delayed.

Numerous federal, state and international laws address privacy, data protection and the collection, storing, sharing, use, disclosure and protection of personally identifiable information and other user data. Numerous states already have, and are looking to expand, data protection legislation. For example, in 2018, California enacted the California Consumer Privacy Act (“CCPA”), which became effective on January 1, 2020. The CCPA gives California residents expanded privacy rights and protections, and provides civil penalties for violations and a private right of action for data breaches. Outside the United States, personally identifiable information and other user data is increasingly subject to legislation and regulations in numerous jurisdictions around the world, the intent of which is to protect the privacy of information that is collected, processed and transmitted in or from the governing jurisdiction. Foreign data protection, privacy, information security, user protection and other laws and regulations are often more restrictive than those in the United States. In particular, the EU and its member states traditionally have taken broader views as to types of data that are subject to privacy and data protection laws and regulations, and have imposed greater legal obligations on companies in this regard. For example, in April 2016, European legislative bodies adopted the General Data Protection Regulation (“GDPR”), which became effective May 25, 2018. The GDPR applies to any company established in the EU as well as to those outside the EU if they collect and use personal data of EU residents. The GDPR enhances data protection obligations for processors and controllers of personal data, including, for example, expanded disclosures about how personal information is to be used, limitations on retention of

information, mandatory data breach notification requirements and onerous new obligations on services providers. Non-compliance with the GDPR may result in monetary penalties of up to €20 million or 4% of annual worldwide revenue, whichever is higher. While we have taken steps to comply with the GDPR, including reviewing our security procedures, updating our website, revising our clinical trial informed consents, and entering into data processing agreements with relevant contractors, we cannot assure you that our efforts to remain in compliance will be fully successful. The GDPR and other changes in laws or regulations associated with the enhanced protection of personal data may increase our costs of compliance and result in greater legal risks.

Foreign currency exchange rates may adversely affect our results.

Due to our operations outside of the United States, we are exposed to market risk, related to changes in foreign currency exchange rates. Historically, we have not hedged our foreign currency exposure. Changes in the relative values of currencies occur regularly and, in some instances, could materially adversely affect our business, our financial condition, the results of our operations or our cash flows.

For the years ended December 31, 2020 and 2019, changes in foreign currency exchange rates did not have a material impact on our historical financial position, our business, our financial condition, the results of our operations or our cash flows. A hypothetical 10% change in foreign currency rates would not have a material impact on our historical financial position or results of operations. However, there can be no assurance that changes in foreign currency exchange rates will not have a material adverse impact on us in the future.

The effects of the Tax Cuts and Jobs Act and future changes in tax laws could adversely affect our business and financial conditions.

The Tax Cuts and Jobs Act (the "Tax Act") significantly reformed the Internal Revenue Code of 1986, as amended. The Tax Act, among other things, included changes to U.S. federal tax rates, imposed significant additional limitations on the deductibility of interest and net operating loss carryforwards, allowed for the expensing of capital expenditures, and put into effect the migration from a "worldwide" system of taxation to a territorial system. These changes and other aspects of the Tax Act remain subject to developing interpretation and clarification. Further, the new administration could introduce modifications, technical corrections or clarifications to the Tax Act or other changes in tax laws. Increases in tax rates or modifications and changes in tax laws, including the Tax Act, could materially and adversely affect our business and financial conditions.

Inadequate funding for the FDA, the SEC and other government agencies, or a work slowdown or stoppage at those agencies as part of a broader federal government shutdown, 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, the ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of the SEC and other government agencies on which our operations may rely, including those that fund research and development activities, is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including beginning on December 22, 2018, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical FDA, SEC and other government employees and stop critical activities. Additionally, FDA and regulatory authorities outside the United States may various restrictions or other policy measures in response to the COVID-19 pandemic. If a prolonged government shutdown or slowdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, future government shutdowns could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations.

Risks Related to Our Intellectual Property

If we are not able to obtain and enforce market exclusivity for our technologies or product candidates, development and commercialization of our product candidates may be adversely affected.

In our industry, the majority of an innovative product's commercial value is usually realized during the period in which it has market exclusivity. Market exclusivity is comprised of both patent and other intellectual property protection, as well as regulatory exclusivity.

In the United States and some other countries, when market exclusivity expires and generic versions of a product are approved and marketed, there usually are very substantial and rapid declines in the product's sales. Accordingly, our success depends in part on our ability to obtain and maintain patents and other forms of intellectual property rights, including trademarks, trade secrets and in-licenses of intellectual property rights of others, for our product candidates and platform technologies, methods used to manufacture our product candidates, methods of patient stratification and methods for treating patients using our product candidates, as well as our ability to preserve our trade secrets, to prevent third parties from infringing upon our proprietary rights and to operate without infringing upon the proprietary rights of others. Certain research and development activities involved in pharmaceutical development are exempt from patent infringement in the United States and other jurisdictions, for example, in the U.S. by the provisions of 35 U.S.C. § 271(e)(1) (the "Safe Harbor"). However, in the U.S. and certain other jurisdictions, the Safe Harbor exemption terminates when the sponsor submits an application for marketing approval (e.g., a New Drug Application ("NDA") in the U.S.). Therefore, the risk that a third party might allege patent infringement may increase as our products approach commercialization. We may not be able to apply for patents or obtain patent protection on certain aspects of our product candidates or our platform in a timely fashion or at all. Our existing issued and granted patents and any future patents we obtain may not be sufficiently broad to prevent others from using our technology or from developing competing products and technology. There is no guarantee that any of our pending patent applications will result in issued or granted patents, that any of our issued or granted patents will not later be found to be invalid or unenforceable, or that any issued or granted patents will include claims that are sufficiently broad to cover our product candidates, our platform technologies, or any methods relating to them, or to provide meaningful protection from our competitors. Moreover, the patent position of biotechnology and pharmaceutical companies can be highly uncertain and involves complex legal and factual questions. We will be able to protect our proprietary rights from unauthorized use by third parties only to the extent that our current and future proprietary technology and product candidates are covered by valid and enforceable patents or are effectively maintained as trade secrets. If third parties disclose or misappropriate our proprietary rights, it may materially and adversely impact our position in the market.

Legal issues related to the patentability of biopharmaceuticals, and methods of their manufacture and use, are complex and uncertain in some countries. In some countries, applicants are not able to protect methods of treating human beings or medical treatment processes. Intellectual property protection varies throughout the world and is subject to change over time. Certain jurisdictions have enacted various rules and laws precluding issuance of patents encompassing any methods a doctor may practice on a human being or any other animal to treat a disease or condition. Further, many countries have enacted laws and regulatory regimes that do not allow patent protection for methods of use of known compounds. Particularly given that some of our product candidates may represent stereopure versions of previously described oligonucleotides, it may be difficult or impossible to obtain patent protection for them in relevant jurisdictions. Thus, in some countries and jurisdictions, it may not be possible to patent some of our product candidates at all. In some countries and jurisdictions, only composition claims may be obtained, and only when those compositions are or contain compounds that are new and/or novel. Also, patents issued with composition claims (*i.e.*, covering product candidates) cannot always be enforced to protect methods of using those compositions to treat or diagnose diseases or medical conditions. In such countries or jurisdictions, enforcement of patents to protect our product candidates, or their uses, may be difficult or impossible. Lack of patent protection in such cases may have a materially adverse effect on our business and financial condition.

Furthermore, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates, their manufacture or their use might expire before or shortly after those candidates receive regulatory approval and are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. We expect to seek extensions of patent terms where these are available upon regulatory approval in those countries where we are prosecuting patents. This includes in the United States under the Drug Price Competition and Patent Term Restoration Act of 1984, which permits a patent term extension of up to five years beyond the expiration of the patent. However, the applicable authorities, including the FDA in the United States, and any equivalent regulatory authority in other countries, may not agree with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. If this occurs, our competitors may take advantage of our investment in development and clinical trials by referencing our clinical and preclinical data and launch their product earlier than might otherwise be possible.

The U.S. Patent and Trademark Office ("USPTO") and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent prosecution process. There are situations in which noncompliance can result in abandonment or lapse of a patent or patent application, or loss of right to enforce patent claims, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, competitors might be able to enter the market earlier than would otherwise have been the case. The standards applied by the USPTO and foreign patent offices in granting patents are not uniform, can vary substantially from country to country, and are not always applied predictably, requiring country-specific patent expertise in each jurisdiction in which patent protection is sought. For example, there is no uniform worldwide policy regarding patentable subject matter or the scope of claims allowable in biotechnology and pharmaceutical patents. As such, we do not know the degree of future protection that we will have on our proprietary products and technologies. While we will endeavor to try to protect our product candidates and platform technology with intellectual property rights such as patents, as appropriate, the process of filing and prosecuting patent applications, and obtaining, maintaining and defending patents is time-consuming, expensive, uncertain, and sometimes unpredictable.

In addition, there are numerous recent changes to the patent laws and proposed changes to the rules of the USPTO that may have a significant impact on our ability to protect our technology and enforce our intellectual property rights. For example, the America Invents Act, enacted within the last several years, involves significant changes in patent legislation. The U.S. Supreme Court has ruled on several patent cases in recent years, some of which cases either narrow the scope of patent protection available in certain circumstances or weaken the rights of patent owners in certain situations. The decision by the U.S. Supreme Court in *Association for Molecular Pathology v. Myriad Genetics, Inc.* precludes a claim to a nucleic acid having a stated nucleotide sequence which is identical to a sequence found in nature and unmodified. We currently are not aware of an immediate impact of this decision on our patents or patent applications because we are developing oligonucleotides which contain modifications that we believe are not found in nature. However, this decision has yet to be clearly interpreted by courts and by the USPTO. We cannot make assurances that the interpretations of this decision or subsequent rulings will not adversely impact our patents or patent applications. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

Once granted, patents may remain open to opposition, interference, re-examination, post-grant review, *inter partes* review, nullification or derivation action in court or before patent offices or similar proceedings for a given period after allowance or grant, during which time third parties can raise objections against such initial grant. In the course of such proceedings, which may continue for a protracted period of time, the patent owner may be compelled to limit the scope of the allowed or granted claims attacked or may lose the allowed or granted claims altogether. In addition, there can be no assurance that:

- Others will not or may not be able to make, use or sell compounds that are the same as or similar to our product candidates but that are not covered by the claims of the patents that we own or license.
- We or our licensors, collaborators or any future collaborators are the first to make the inventions covered by each of our issued patents and pending patent applications that we own or license.
- We or our licensors, collaborators or any future collaborators are the first to file patent applications covering certain aspects of our inventions.
- Others will not independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights.
- A third party may not challenge, invalidate, circumvent or weaken our patents, or that, if any of these events should occur, that a court would hold that our patents are valid, enforceable and infringed.
- Any issued patents that we own or have licensed will provide us with any competitive advantages, or will not be challenged, invalidated, circumvented or weakened by third parties.
- We may develop additional proprietary technologies that are patentable.
- The patents of others will not have an adverse effect on our business.
- Our competitors do not conduct research and development activities in countries where we do not have enforceable patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets.

We license patent rights from third-party owners or licensees. If such owners or licensees do not properly or successfully obtain, maintain or enforce the patents underlying such licenses, or if they retain or license to others any competing rights, our competitive position and business prospects may be adversely affected.

We license patent rights from third parties that we may use from time to time to protect certain aspects of our technology and programs. We may license additional third-party intellectual property in the future. To the extent that we use, and ultimately rely on, in-licensed technologies in our platform and our programs, our success will depend in part on the ability of our licensors to obtain, maintain and enforce patent protection for those in-licensed technologies. Our licensors may not successfully prosecute the patent applications licensed to us. Even if patents issue or are granted, our licensors may fail to maintain these patents, may determine not to pursue litigation against other companies that are infringing these patents, or may pursue litigation less aggressively than we would. Further, we may not obtain exclusive rights, which would allow for third parties to develop competing products. Without protection for, or exclusive right to, the intellectual property we license, other companies might be able to offer substantially identical products for sale, which could adversely affect our competitive business position and harm our business prospects. In addition, we may sublicense our rights under our third-party licenses to current or future collaborators or any future strategic partners. Any impairment of these sublicensed rights could result in reduced revenue under any future collaboration agreements we may enter into or result in termination of an agreement by one or more of our current or future collaborators or any future strategic partners.

Other companies or organizations may challenge our or our licensors' patent rights or may assert patent rights that prevent us from developing and commercializing our products.

Nucleic acid therapeutics is a relatively new scientific field, the commercial exploitation of which has resulted in many different patents and patent applications from organizations and individuals seeking to obtain patent protection in the field. We have obtained grants and issuances of patents in this field. The issued patents and pending patent applications in the United States and in key markets around the world that we own or license claim certain methods, compositions and processes relating to the discovery, development, manufacture and/or commercialization of oligonucleotides and/or our platform.

As the field of oligonucleotides matures, patent applications are being processed by national patent offices around the world. There is uncertainty about which patents will issue, and, if they do, as to when, to whom, and with what claims. It is likely that there will be significant litigation in the courts and other proceedings, such as interference, reexamination and opposition proceedings, in various patent offices relating to patent rights in the oligonucleotides field. In many cases, the possibility of appeal or opposition exists for either us or our opponents, and it may be years before final, unappealable rulings are made with respect to these patents in certain jurisdictions. The timing and outcome of these and other proceedings is uncertain and may adversely affect our business, particularly if we are not successful in defending the patentability and scope of our pending and issued patent claims or if third parties are successful in obtaining claims that cover any of our product candidates or our platform. In addition, third parties may attempt to invalidate our intellectual property rights. Even if our rights are not directly challenged, invalidated or circumvented, disputes could lead to the weakening of our intellectual property rights. Our defense against any attempt by third parties to challenge, invalidate, circumvent or weaken our intellectual property rights could be costly to us, could require significant time and attention of our management and could adversely affect our business and our ability to successfully compete in the field of oligonucleotides.

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

Obtaining a valid and enforceable issued or granted patent covering our technology in the United States and worldwide can be extremely costly. In jurisdictions where we have not obtained patent protection, competitors may use our technology to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but where it is more difficult to enforce a patent as compared to the United States. Competitor products may compete with our future products in jurisdictions where we do not have issued or granted patents or where our issued or granted patent claims or other intellectual property rights are not sufficient to prevent competitor activities in these jurisdictions. The legal systems of certain countries, particularly certain developing countries, make it difficult to enforce patents and such countries may not recognize other types of intellectual property protection, particularly relating to biopharmaceuticals. This could make it difficult for us to prevent the infringement of our patents or marketing of competing products in violation of our proprietary rights generally in certain jurisdictions. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial cost and divert our efforts and attention from other aspects of our business.

We generally file a provisional patent application first (a priority filing) at the USPTO. A Patent Cooperation Treaty ("PCT") application is usually filed within 12 months after the priority filing. Regional and/or national patent applications may be pursued outside of the United States, either based on a PCT application or as a direct filing, in some cases claiming priority to a prior U.S. or PCT filing. Some of our cases have been filed in multiple jurisdictions, including major market jurisdictions. We also commonly enter the national stage in the United States through a PCT filing. We have so far not filed for patent protection in all national and regional jurisdictions where such protection may be available. In addition, we may decide to abandon national and regional patent applications before grant. Finally, the grant proceeding of each national or regional patent is an independent proceeding which may lead to situations in which applications might in some jurisdictions be refused by the relevant registration authorities, while granted by others. It is also quite common that depending on the country, different scopes of patent protection may be granted on the same product or technology.

The laws of some jurisdictions do not protect intellectual property rights to the same extent as the laws in the United States, and many companies have encountered significant difficulties in protecting and defending such rights in such jurisdictions. If we or our licensors encounter difficulties in protecting, or are otherwise precluded from effectively protecting, the intellectual property rights important for our business in such jurisdictions, the value of these rights may be diminished and we may face additional competition from others in those jurisdictions. Many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties, allowing competitors to manufacture and sell their own versions of our product, thereby reducing our sales. In addition, many countries do not permit enforcement of patents, or 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 a patent. If we or any of our licensors, collaborators or present or future partners are forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position in the relevant jurisdiction may be impaired and our business and results of operations may be adversely affected.

The requirements for patentability may differ in certain countries. For example, some jurisdictions may have heightened requirements for patentability compared to others, and may specifically require a detailed description of medical uses of a claimed drug. In some jurisdictions, unlike the United States, there is no link between regulatory approval of a drug and its patent status. Furthermore, generic or biosimilar drug manufacturers or other competitors may challenge the scope, validity or enforceability of our or our licensors' or collaborators' patents, requiring us or our licensors or collaborators to engage in complex, lengthy and costly litigation or other proceedings. Generic or biosimilar drug manufacturers may develop, seek approval for, and launch generic versions of our products. Accordingly, our and our licensors' and collaborators' efforts to enforce intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we own or license.

We or our licensors, collaborators or any future strategic partners may become subject to third party claims or litigation alleging infringement of patents or other proprietary rights or seeking to invalidate patents or other proprietary rights, and we may need to resort to litigation to protect or enforce our patents or other proprietary rights, all of which could be costly and time consuming, or delay or prevent the development and commercialization of our product candidates, or put our patents and other proprietary rights at risk.

We or our licensors, collaborators or any future strategic partners may be subject to third-party claims for infringement or misappropriation of patent or other proprietary rights. We are generally obligated under our license or collaboration agreements to indemnify and hold harmless our licensors or collaborators for damages arising from intellectual property infringement by us. If we or our licensors, collaborators or any future strategic partners are found to infringe a third-party patent or other intellectual property rights, we could be required to pay damages, potentially including treble damages, if we are found to have willfully infringed. In addition, we or our licensors, collaborators or any future strategic partners may choose to seek, or be required to seek, a license from a third party, which may not be available on acceptable terms, if at all. Even if a license can be obtained on acceptable terms, the rights may be non-exclusive, which could give our competitors access to the same technology or intellectual property rights licensed to us. If we fail to obtain a required license, we or our collaborator, or any future collaborator, may be unable to effectively market product candidates based on our technology, which could limit our ability to generate revenue or achieve profitability and possibly prevent us from generating revenue sufficient to sustain our operations. In addition, we may find it necessary to pursue claims or initiate lawsuits to protect or enforce our patent or other intellectual property rights. The cost to us in defending or initiating any litigation or other proceeding relating to patent or other proprietary rights, even if resolved in our favor, could be substantial, and litigation would divert our management's attention. Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could delay our research and development efforts and limit our ability to continue our operations.

If we were to initiate legal proceedings against a third party to enforce a patent covering one of our products or our technology, the defendant could counterclaim that our patent is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, for example, lack of novelty, lack of written disclosure, 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. The outcome following legal allegations of invalidity and unenforceability during patent litigation is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we and the patent examiner were unaware during prosecution. If a defendant 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 one or more of our products or certain aspects of our platform technology. Such a loss of patent protection could negatively impact our business. Patents and other intellectual property rights also will not protect our technology if competitors design around our protected technology without legally infringing our patents or other intellectual property rights.

Intellectual property rights of third parties could adversely affect our ability to commercialize our product candidates, and we might be required to litigate or obtain licenses from third parties in order to develop or market our product candidates. Such litigation or licenses could be costly or not available on commercially reasonable terms.

Because the oligonucleotide intellectual property landscape is still evolving and our product candidates have not yet reached commercialization, it is difficult to conclusively assess our freedom to operate. There are numerous companies that have pending patent applications and issued patents directed to certain aspects of oligonucleotides. We are aware of third-party competitors in the oligonucleotide therapeutics space, whose patent filings and/or issued patents may include claims directed to targets and/or products related to some of our programs. It is possible that at the time that we commercialize our products these third-party patent portfolios may include issued patent claims that cover our products or critical features of their production or use. Our competitive position may suffer if patents issued to third parties or other third-party intellectual property rights cover, or may be alleged to cover, our products or elements thereof, or methods of manufacture or use relevant to our development plans. In such cases, we may not be in a position to develop or commercialize product candidates unless we successfully pursue litigation to nullify or invalidate the third party intellectual property right concerned or enter into a license agreement with the intellectual property right holder, if available on commercially reasonable terms.

It is also possible that we have failed to identify relevant third-party patents or applications. For example, U.S. applications filed before November 29, 2000, and certain U.S. applications filed after that date that will not be filed outside the United States remain confidential until patents issue. Patent applications in the United States and elsewhere are published approximately 18 months after the earliest filing date for which priority is claimed, with such earliest filing date being commonly referred to as the priority date. Therefore, patent applications covering our products or platform technology could have been filed by others without our knowledge. Additionally, pending patent applications which have been published can, subject to certain limitations, be later amended in a manner that could cover our platform technologies, our products or the use of our products. Third party intellectual property right holders may also actively bring infringement claims against us. We cannot guarantee that we will be able to successfully settle or otherwise resolve such infringement claims. If we are unable to successfully settle future claims on terms acceptable to us, we may be required to engage in or continue costly, unpredictable and time-consuming litigation and may be prevented from or experience substantial delays in marketing our products. If we fail in any such dispute, in addition to being forced to pay damages, we may be temporarily or permanently prohibited from commercializing any of our product candidates that are held to be infringing. We might, if possible, also be forced to redesign product candidates so that we no longer infringe the third-party intellectual property rights. Any of these events, even if we were ultimately to prevail, could require us to divert substantial financial and management resources that we would otherwise be able to devote to our business.

If we fail to comply with our obligations under any license, collaboration or other agreement, we may be required to pay damages and could lose intellectual property rights that are necessary for developing and protecting our product candidates, or we could lose certain rights to grant sublicenses.

There are many issued patents and/or pending patent applications that claim aspects of oligonucleotide compositions, chemistry and/or modifications that we may want or need to apply to our product candidates. There are also many issued patents and/or pending patent applications that claim targeted genes or portions of genes that may be relevant for the oligonucleotides we wish to develop. We are aware of third-party competitors in the oligonucleotide therapeutics space whose patent filings and/or issued patents may include claims directed to targets and/or product candidates related to some of our development programs. It is possible that these third-party patent portfolios may include issued patent claims that cover our product candidates or critical features of their production or use. Thus, it is possible that one or more organizations will hold patent rights to which we will need or want a license. If those organizations refuse to grant us a license to such patent rights on reasonable terms, or at all, we may not be able to market products or perform research and development or other activities covered by these patents.

Our technology licenses and any future licenses we enter into are likely to impose various development, commercialization, funding, milestone, royalty, diligence, sublicensing, insurance, patent prosecution and enforcement, and/or other obligations on us. If we breach any of these imposed obligations, or use the intellectual property licensed to us in an unauthorized manner, we may be required to pay damages and the licensor may have the right to terminate the license, which could result in us being unable to develop, manufacture and sell products that are covered by the licensed technology or enable a competitor to gain access to the licensed technology. Moreover, our licensors may own or control intellectual property that has not been licensed to us and, as a result, we may be subject to claims, regardless of their merit, that we are infringing or otherwise violating the licensor’s rights. In addition, while we cannot currently determine the amount of the royalty obligations we would be required to pay on sales of future products, if any, the amounts may be significant. The amount of our future royalty obligations will depend on the technology and intellectual property we use in products that we successfully develop and commercialize, if any. Therefore, even if we successfully develop and commercialize products, we may be unable to achieve or maintain profitability.

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

In addition to seeking patent protection for certain aspects of our product candidates, we also consider trade secrets, including confidential and unpatented know-how, improvements and technological innovation important to the maintenance of our competitive position. We protect trade secrets and confidential and unpatented know-how, improvements and technological innovation, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to such knowledge, 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 that obligate them to maintain confidentiality and assign their inventions to us. Despite these 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 in the United States and certain foreign jurisdictions 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, 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, our competitive position would be harmed.

We may be subject to claims that we or our employees or consultants have wrongfully used or disclosed alleged trade secrets of our employees' or consultants' former employers or their clients. These claims may be costly to defend and if we do not successfully do so, we may be required to pay monetary damages and may lose valuable intellectual property rights or personnel.

Many of our employees were previously employed at universities or biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although no claims against us are currently pending, we may be subject to claims that these employees or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers. Litigation may be necessary to defend against these claims. If we fail in defending such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. A loss of key research personnel or their work product could hamper our ability to commercialize, or prevent us from commercializing, our product candidates, which could severely harm our business. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management.

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 trademarks or trade names may be infringed, challenged, invalidated, circumvented, weakened 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 or may be forced to stop using these names, which we need for name recognition by potential partners or customers in our markets of interest. If we are unable to establish name recognition based on our trademarks and trade names, we may not be able to compete effectively and our business may be adversely affected.

Risks Related to Our Being a Singapore Company

We are a Singapore incorporated company and it may be difficult to enforce a judgment of U.S. courts for civil liabilities under U.S. federal securities laws against us, our directors or officers in Singapore.

We are incorporated under the laws of the Republic of Singapore, and certain of our directors are residents outside the United States. Moreover, a significant portion of our consolidated assets are located outside the United States. Although we are incorporated outside the United States, we have agreed to accept service of process in the United States through our agent designated for that purpose. Nevertheless, because a majority of the consolidated assets owned by us are located outside the United States, any judgment obtained in the United States against us may not be enforceable within the United States.

There is no treaty between the United States and Singapore providing for the reciprocal recognition and enforcement of judgments in civil and commercial matters and a final judgment for the payment of money rendered by any federal or state court in the United States based on civil liability, whether or not predicated solely upon the federal securities laws, would, therefore, not be automatically enforceable in Singapore. There is uncertainty as to whether judgments of courts in the United States based upon the civil liability provisions of the federal securities laws of the United States would be recognized or enforceable in Singapore. In addition, holders of book-entry interests in our shares will be required to be registered shareholders as reflected in our shareholder register in order to have standing to bring a shareholder action and, if successful, to enforce a foreign judgment against us, our directors or our executive officers in the Singapore courts. The administrative process of becoming a registered holder could result in delays prejudicial to any legal proceedings or enforcement action. Consequently, it may be difficult for investors to enforce against us, our directors or our officers in Singapore judgments obtained in the United States which are predicated upon the civil liability provisions of the federal securities laws of the United States.

We are incorporated in Singapore and our shareholders may have more difficulty in protecting their interests than they would as shareholders of a corporation incorporated in the United States.

Our corporate affairs are governed by our constitution and by the laws governing corporations incorporated in Singapore. The rights of our shareholders and the responsibilities of the members of our board of directors under Singapore law are different from those applicable to a corporation incorporated in the United States. Principal shareholders of Singapore companies do not owe fiduciary duties to minority shareholders, as compared, for example, to controlling shareholders in corporations incorporated in Delaware. Our public shareholders may have more difficulty in protecting their interests in connection with actions taken by our management, members of our board of directors or our principal shareholders than they would as shareholders of a corporation incorporated in the United States.

In addition, only persons who are registered as shareholders in our shareholder register are recognized under Singapore law as shareholders of our company. Only registered shareholders have legal standing to institute shareholder actions against us or otherwise seek to enforce their rights as shareholders. Investors in our shares who are not specifically registered as shareholders in our shareholder register (for example, where such shareholders hold shares indirectly through the Depository Trust Company) are required to become registered as shareholders in our shareholder register in order to institute or enforce any legal proceedings or claims against

us, our directors or our executive officers relating to shareholder rights. Holders of book-entry interests in our shares may become registered shareholders by exchanging their book-entry interests in our shares for certificated shares and being registered in our shareholder register. Such process could result in administrative delays which may be prejudicial to any legal proceeding or enforcement action.

We are subject to the laws of Singapore, which differ in certain material respects from the laws of the United States.

As a company incorporated under the laws of the Republic of Singapore, we are required to comply with the laws of Singapore, certain of which are capable of extra-territorial application, as well as our constitution. In particular, we are required to comply with certain provisions of the Securities and Futures Act of Singapore (Cap 289) (the "SFA"), which prohibit certain forms of market conduct and require certain information disclosures, and impose criminal and civil penalties on corporations, directors and officers in respect of any breach of such provisions. We are required to comply with the Singapore Code on Take-Overs and Mergers (the "Singapore Takeover Code"), which specifies, among other things, certain circumstances in which a general offer is to be made upon a change in effective control, and further specifies the manner and price at which voluntary and mandatory general offers are to be made.

We are also subject to Section 34 of the Singapore Patents Act, which provides that a person residing in Singapore is required to obtain written authorization from the Singapore Registrar of Patents (the "Registrar") before filing an application for a patent for an invention outside of Singapore, unless certain conditions have been satisfied. A violation of Section 34 is a criminal offense punishable by a fine not exceeding S$5,000, or imprisonment for a term not exceeding two years, or both. There have been some instances where we have undertaken filings outside of Singapore, and there may be instances where we are required to make such filings in the future, without first obtaining written authorization from the Registrar. We have notified the Registrar of such filings and we have since implemented measures to address the requirements of Section 34 moving forward. To date, the Registrar has offered a compound of some of the offences considered against payment of a sum of S$50 to S$ 100 per considered case. Under Singapore law, the Registrar has discretion to offer a compound of such offences against payment of a sum of money of up to S$2,000, or to prosecute the offence subject to the other penalties noted above. There remain approximately 40 patent applications in multiple patent families which we have notified the Intellectual Property Office of Singapore ("IPOS") of where Section 34 requirements have not been complied with, and are pending IPOS' decision thereon. We cannot assure you that the Registrar will offer to compound any such violations of Section 34, or that any offer to compound will be for an amount similar to previous compound offers.

The laws of Singapore and of the United States differ in certain significant respects. The rights of our shareholders and the obligations of our directors and officers under Singapore law (including under the Companies Act of Singapore (Cap 50) (the "Singapore Companies Act") are different from those applicable to a company incorporated in the State of Delaware in material respects, and our shareholders may have more difficulty and less clarity in protecting their interests in connection with actions taken by our management, members of our board of directors or our controlling shareholders than would otherwise apply to a company incorporated in the State of Delaware.

The application of Singapore law, in particular, the Singapore Companies Act may, in certain circumstances, impose more restrictions on us and our shareholders, directors and officers than would otherwise be applicable to a company incorporated in the State of Delaware. For example, the Singapore Companies Act requires directors to act with a reasonable degree of diligence and, in certain circumstances, imposes criminal liability for specified contraventions of particular statutory requirements or prohibitions. In addition, pursuant to the provisions of the Singapore Companies Act, shareholders holding 10% or more of the total number of paid-up shares carrying the right of voting in general meetings may require the convening of an extraordinary general meeting of shareholders by our directors. If our directors fail to comply with such request within 21 days of the receipt thereof, the original requisitioning shareholders, or any of them holding more than 50% of the voting rights represented by the original requisitioning shareholders, may proceed to convene such meeting, and we will be liable for the reasonable expenses incurred by such requisitioning shareholders. We are also required by the Singapore Companies Act to deduct such corresponding amounts from fees or other remuneration payable by us to such non-complying directors.

We are subject to the Singapore Takeover Code, which requires a person acquiring 30% or more of our voting shares to conduct a takeover offer for all of our voting shares. This could have the effect of discouraging, delaying or preventing a merger or acquisition and limit the market price of our ordinary shares.

We are subject to the Singapore Takeover Code. The Singapore Takeover Code contains provisions that may delay, deter or prevent a future takeover or change in control of our company and limit the market price of our ordinary shares for so long as we remain a public company with more than 50 shareholders and net tangible assets of S$5 million (Singapore dollars) or more. For example, under the Singapore Takeover Code, any person acquiring, whether by a series of transactions over a period of time or not, either on such person's own or together with parties acting in concert with such person, 30% or more of our voting shares, or if such person holds, either on such person's own or together with parties acting in concert with such person, between 30% and 50% (both inclusive) of our voting shares, and if such person (or parties acting in concert with such person) acquires additional voting shares representing

more than 1% of our voting shares in any six-month period, must, except with the consent of Securities Industry Council in Singapore, extend a takeover offer for our remaining voting shares in accordance with the Singapore Takeover Code. Therefore, any investor seeking to acquire a significant stake in our company may be deterred from doing so if, as a result, such investor would be required to conduct a takeover offer for all of our voting shares.

These same provisions could discourage potential investors from acquiring a stake or making a significant investment in our company and may substantially impede the ability of our shareholders to benefit from a change of effective control and, as a result, may adversely affect the market price of our ordinary shares and the ability to realize any benefits from a potential change of control.

For a limited period of time, our directors have general authority to allot and issue new ordinary shares on terms and conditions and for such purposes as may be determined by our board of directors in its sole discretion.

Under Singapore law, we may only allot and issue new shares with the prior approval of our shareholders in a general meeting. At our most recent annual general meeting of shareholders, our shareholders provided our directors with a general authority, subject to the provisions of the Singapore Companies Act and our constitution, to allot and issue any number of new ordinary shares and/or make or grant offers, agreements, options or other instruments (including the grant of awards or options pursuant to our equity-based incentive plans and agreements in effect from time to time) that might or would require ordinary shares to be allotted and issued (collectively, the "Instruments"); and unless revoked or varied by the Company in a general meeting, such authority will continue in force until the earlier of (i) the conclusion of our next annual general meeting of shareholders, or (ii) the expiration of the period within which our next annual general meeting of shareholders is required by law to be held. Subject to the general requirements of the Singapore Companies Act and our constitution, the general authority given to our directors by our shareholders to allot and issue ordinary shares and/or make or grant the Instruments may be exercised by our directors on such terms and conditions, for such purposes and for consideration as they may in their sole discretion deem fit, and with such rights or restrictions as they may think fit to impose and as are set forth in our constitution. Any additional issuances of new ordinary shares and/or any grant of the Instruments by our directors may dilute our shareholders' interests in our ordinary shares and/or adversely impact the market price of our ordinary shares.

We may be or become a passive foreign investment company, which could result in adverse U.S. federal income tax consequences to U.S. Holders.

The rules governing passive foreign investment companies ("PFICs") can have adverse effects for U.S. federal income tax purposes. The tests for determining PFIC status for a taxable year depend upon the relative values of certain categories of assets and the relative amounts of certain kinds of income. The determination of whether we are a PFIC, which must be made annually after the close of each taxable year, depends on the particular facts and circumstances (such as the valuation of our assets, including goodwill and other intangible assets) and may also be affected by the application of the PFIC rules, which are subject to differing interpretations. The fair market value of our assets is expected to relate, in part, to (a) the market price of our ordinary shares and (b) the composition of our income and assets, which will be affected by how, and how quickly, we spend any cash that is raised in any financing transaction. Moreover, our ability to earn specific types of income that we currently treat as non-passive for purposes of the PFIC rules is uncertain with respect to future years. Because the value of our assets for purposes of determining PFIC status will depend in part on the market price of our ordinary shares, which may fluctuate significantly, there can be no assurance that we will not be considered a PFIC for our current taxable year ending December 31, 2021 or for any future taxable year.

If we are a PFIC, a U.S. Holder (defined below) would be subject to adverse U.S. federal income tax consequences, such as ineligibility for any preferred tax rates on capital gains or on actual or deemed dividends, interest charges on certain taxes treated as deferred, and additional reporting requirements under U.S. federal income tax laws and regulations. A U.S. Holder may in certain circumstances mitigate adverse tax consequences of the PFIC rules by filing an election to treat the PFIC as a qualified electing fund ("QEF") or, if shares of the PFIC are "marketable stock" for purposes of the PFIC rules, by making a mark-to-market election with respect to the shares of the PFIC. We do not intend to comply with the reporting requirements necessary to permit U.S. Holders to elect to treat us as a QEF. If a U.S. Holder makes a mark-to-market election with respect to its ordinary shares, the U.S. Holder is required to include annually in its U.S. federal taxable income an amount reflecting any year end increase in the value of its ordinary shares. For purposes of this discussion, a "U.S. Holder" is a beneficial owner of ordinary shares that is for U.S. federal income tax purposes: (i) an individual who is a citizen or resident of the United States; (ii) a corporation (or other entity taxable as a corporation for U.S. federal income tax purposes) created or organized in or under the laws of the United States, any state thereof or the District of Columbia; (iii) an estate the income of which is subject to U.S. federal income taxation regardless of its source; or (iv) a trust (a) if a court within the U.S. can exercise primary supervision over its administration, and one or more U.S. persons have the authority to control all of the substantial decisions of that trust, or (b) that was in existence on August 20, 1996, and validly elected under applicable Treasury Regulations to continue to be treated as a domestic trust.

Investors should consult their own tax advisors regarding all aspects of the application of the PFIC rules to the ordinary shares.

Singapore taxes may differ from the tax laws of other jurisdictions.

Prospective investors should consult their tax advisors concerning the overall tax consequences of purchasing, owning and disposing of our shares. Singapore tax law may differ from the tax laws of other jurisdictions, including the United States.

We may become subject to unanticipated tax liabilities.

We are incorporated under the laws of Singapore. We are, however, subject to income, withholding or other taxes in certain jurisdictions by reason of our activities and operations, and it is also possible that tax authorities in any such jurisdictions could assert that we are subject to greater taxation than we currently anticipate. Any such non-Singaporean tax liability could materially adversely affect our results of operations.

Tax authorities could challenge the allocation of income and deductions among our subsidiaries, which could increase our overall tax liability.

We are organized in Singapore, and we currently have subsidiaries in the United States, Japan, the United Kingdom, and Ireland. As we grow our business, we conduct, and expect to continue to conduct, increased operations through our subsidiaries in various jurisdictions. If two or more affiliated companies are located in different jurisdictions, the tax laws or regulations of each country generally will require transactions between those affiliated companies to be conducted on terms consistent with those between unrelated companies dealing at arms' length, and appropriate documentation generally must be maintained to support the transfer prices. We maintain our transfer pricing policies to be compliant with applicable transfer pricing laws, but our transfer pricing procedures are not binding on applicable tax authorities.

If tax authorities were to successfully challenge our transfer pricing, there could be an increase in our overall tax liability, which could adversely affect our financial condition, results of operations and cash flows. In addition, the tax laws in the jurisdictions in which we operate are subject to differing interpretations. Tax authorities may challenge our tax positions, and if successful, such challenges could increase our overall tax liability. In addition, the tax laws in the jurisdictions in which we operate are subject to change. We cannot predict the timing or content of such potential changes, and such changes could increase our overall tax liability, which could adversely affect our financial condition, results of operations and cash flows.

Our financial results reflect the effect of certain tax credits and the operation of certain tax regimes within the United Kingdom. Recently proposed legislation in the United Kingdom may limit the amount we may be able to claim as a payable tax credit in the future which could impact our financial condition, results of operations and cash flows.

We benefit from the U.K. research and development tax credit regime for small and medium sized companies, whereby our subsidiary in the United Kingdom is able to surrender the trading losses that arise from its research and development activities for a payable tax credit of up to 33.4% of eligible research and development expenditure on staff and consumables. Expenditure of staff supplied by unconnected third parties are eligible for a cash rebate of up to 21.7%.

Due to a recently proposed change in the U.K. legislation affecting the U.K. research and development tax credit regime for small and medium sized companies, our ability to receive a payable tax credit for the surrender of our trading losses from research and development activities incurred from taxable years beginning on or after April 1, 2021 would be limited to the amount equal to three times our "pay as you earn" and U.K. national insurance tax liabilities.

Further, we may not be able to continue to claim a U.K. tax credit for research and development tax credits under the small and medium-sized companies regime in the future if we increase our personnel and expand our business because we may no longer qualify as a small or medium-sized enterprise.

Risks Related to Our Ordinary Shares

The public market for our ordinary shares may not be liquid enough for our shareholders to sell their ordinary shares quickly or at market price, or at all.

Prior to the completion of our initial public offering, there was no public market for our ordinary shares. An active trading market for our shares may not develop or be maintained and our shareholders may not be able to sell their ordinary shares quickly or at the market price, or at all. Our executive officers, our directors and their respective affiliates, and our other significant shareholders beneficially own a significant portion of our outstanding ordinary shares, and therefore, liquidity in our ordinary shares is limited. Due to the limited liquidity in our ordinary shares, relatively small orders can have a disproportionate impact on the trading price of our shares. Further, the limited liquidity in our ordinary shares may also impair our ability to raise capital by conducting offerings of our ordinary shares and may impair our ability to enter into strategic partnerships or acquire companies or products by using our ordinary shares as consideration.

The market price of our ordinary shares is likely to be highly volatile, and our shareholders may lose some or all of their investment.

The market price of our ordinary shares is likely to continue to be highly volatile, including in response to factors that are beyond our control. The stock market in general experiences extreme price and volume fluctuations. In particular, the market prices of securities of pharmaceutical and biotechnology companies are extremely volatile, and experience fluctuations that are often unrelated or disproportionate to the operating performance of these companies. These broad and sector-specific market fluctuations can result in extreme fluctuations in the price of our ordinary shares, regardless of our operating performance, and can cause our shareholders to lose some or all of their investment in the Company.

Our principal shareholders and management own a significant percentage of our ordinary shares and will be able to exert significant control over matters subject to shareholder approval.

Based on information publicly available to us as of December 31, 2020, our executive officers, our directors and their respective affiliates, and our other significant shareholders beneficially own a significant portion of our outstanding ordinary shares. As a result, these shareholders, if acting together, will continue to have significant influence over the outcome of corporate actions requiring shareholder approval, including the election of directors, any merger, consolidation or sale of all or substantially all of our assets and any other significant corporate transaction. The interests of these shareholders may not be the same as or may even conflict with the interests of our other shareholders. For example, these shareholders could delay or prevent a change of control of our company, even if such a change of control would benefit our other shareholders, which could deprive shareholders of an opportunity to receive a premium for their ordinary shares as part of a sale of our company or our assets and might affect the prevailing market price of our ordinary shares. The significant concentration of share ownership may adversely affect the trading price of our ordinary shares due to investors' perception that conflicts of interest may exist or arise.

We incur significant costs due to operating as a public company, and our management is required to devote substantial time to compliance initiatives.

As a public company, we incur significant legal, accounting and other expenses. We are subject to the reporting and other requirements of the Securities Exchange Act of 1934, as amended, or the Exchange Act, the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, and the Dodd-Frank Wall Street Reform and Protection Act, as well as rules subsequently adopted by the SEC and the Nasdaq Stock Market. These rules and regulations require, among other things, that we file annual, quarterly and current reports with respect to our business and financial condition and establish and maintain effective disclosure and financial controls and corporate governance practices. We expect that compliance with these rules and regulations will continue to substantially increase our legal and financial compliance costs and will make some activities more time-consuming and costly, particularly as we are no longer an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012 ("the JOBS Act"). Our management and other personnel devote a substantial amount of time to these compliance requirements.

If we fail to maintain proper and effective internal controls, our ability to produce accurate and timely financial statements could be impaired, which could harm our operating results, our ability to operate our business and investors' views of us.

We are required to comply with Section 404 of the Sarbanes-Oxley Act. Section 404 of the Sarbanes-Oxley Act requires public companies to maintain effective internal control over financial reporting. In particular, we must perform system and process evaluation and testing of our internal control over financial reporting to allow management to report on the effectiveness of our internal control over financial reporting. Ensuring that we have adequate internal financial and accounting controls and procedures in place so that we can produce accurate financial statements on a timely basis is a costly and time-consuming effort that is evaluated frequently. If we fail to maintain the effectiveness of our internal controls or fail to comply in a timely manner with the requirements of the Sarbanes-Oxley Act, or if we identify deficiencies in our internal control over financial reporting that are deemed to be material weaknesses, this could have a material adverse effect on our business. We could lose investor confidence in the accuracy and completeness of our financial reports, which could have an adverse effect on the price of our ordinary shares and we could be subject to sanctions or investigations by Nasdaq, the SEC or other regulatory authorities, which would require additional financial and management resources. In addition, if our efforts to comply with new or changed laws, regulations, and standards differ from the activities intended by regulatory or governing bodies due to ambiguities related to practice, regulatory authorities may initiate legal proceedings against us and our business may be harmed.

The estimates and judgments we make, or the assumptions on which we rely, in preparing our consolidated financial statements could prove inaccurate.

Our consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States (U.S. GAAP). The preparation of these consolidated financial statements requires us to make estimates and judgments that affect the reported amounts of our assets, liabilities, revenues and expenses, the amounts of charges accrued by us and related disclosure of contingent assets and liabilities. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances. We cannot assure, however, that our estimates, or the assumptions underlying them, will not change over time or otherwise prove inaccurate. For example, our estimates as they relate to anticipated timelines and milestones for our clinical trials or preclinical development may prove to be inaccurate. If this is the case, we may be required to restate our consolidated financial statements, which could, in turn, subject us to securities class action litigation. Defending against such potential litigation relating to a restatement of our consolidated financial statements would be expensive and would require significant attention and resources of our management. Moreover, our insurance to cover our obligations with respect to the ultimate resolution of any such litigation may be inadequate. As a result of these factors, any such potential litigation could have a material adverse effect on our financial results, harm our business, and cause our share price to decline.

We do not anticipate paying any cash dividends on our ordinary shares in the foreseeable future.

We have never declared or paid cash dividends on our ordinary shares. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business, and we do not anticipate paying any cash dividends on our ordinary shares in the foreseeable future. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our ordinary shares will be our shareholders' sole source of gain for the foreseeable future.

We may incur significant costs from class action litigation due to share volatility.

Our share price may fluctuate for many reasons, including as a result of public announcements regarding the progress of our development efforts or the development efforts of our collaborators and/or competitors, the addition or departure of our key personnel, variations in our quarterly operating results and changes in market valuations of pharmaceutical and biotechnology companies. Holders of stock which has experienced significant price and trading volatility have occasionally brought securities class action litigation against the companies that issued the stock. If any of our shareholders were to bring a lawsuit of this type against us, even if the lawsuit is without merit, we could incur substantial costs defending the lawsuit. The lawsuit could also divert the time and attention of our management, which could harm our business.

Sales of additional ordinary shares could cause the price of our ordinary shares to decline.

Sales of substantial amounts of our ordinary shares in the public market, or the availability of such shares for sale, by us or others, including the issuance of ordinary shares upon exercise of outstanding options, or the perception that such sales could occur, could adversely affect the price of our ordinary shares. Certain of our shareholders have required us, or have the right to require us, to register the sales of their shares under the Securities Act of 1933, as amended, or the Securities Act, under agreements between us and such shareholders. For example, in August 2019, we filed a registration statement on Form S-3, which was declared effective on August 14, 2019, to register the resale from time to time by certain of our executive officers, directors and their affiliates of up to approximately 7.1 million ordinary shares.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our share price and trading volume could decline.

The trading market for our ordinary shares may depend in part on the research and reports that securities or industry analysts publish about us or our business. If too few securities or industry analysts cover our company, the trading price for our ordinary shares would likely be negatively impacted. If one or more of the analysts who cover us downgrade our ordinary shares or publish inaccurate or unfavorable research about our business, our share price would likely decline. If one or more of these analysts cease coverage of our company or fail to publish reports on us regularly, demand for our ordinary shares could decrease, which might cause our share price and trading volume to decline.

Item 1B. Unresolved Staff Comments

None.

Item 2. Properties

We maintain our U.S. corporate offices and research and development facilities in Cambridge, Massachusetts, where we lease office and laboratory space. In December 2020, we exercised our option to lease an additional 13,126 square feet of the facility and the lease for the additional space is expected to commence on October 1, 2021. The combined space results in a total of approximately 44,000 square feet, which constitutes the entire building.

We lease approximately 90,000 square feet of office and laboratory space in Lexington, Massachusetts, which we use for our research, development and current good manufacturing practice ("cGMP") manufacturing.

We also occupy laboratory and office space in Japan. We believe our existing facilities are adequate to meet our current needs.

Item 3. Legal Proceedings

We are not currently a party to any material legal proceedings.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities

Market Information

Our ordinary shares are traded on the Nasdaq Global Market under the symbol "WVE".

Shareholders

As of February 22, 2021, we had 48,997,368 ordinary shares outstanding and approximately 12 shareholders of record of our ordinary shares.

Unregistered Sales of Securities

Not applicable.

Issuer Purchases of Equity Securities

None.

Item 6. Selected Financial Data

Not applicable.

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

The following discussion and analysis of our financial condition and results of operations should be read in conjunction with our financial statements and related notes appearing elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the "Risk Factors" section of this Annual Report on Form 10-K, our actual results could differ materially from the results described in, or implied by, these forward-looking statements.

COVID-19 Business Update

We are closely monitoring developments related to COVID-19, which was declared a pandemic by the World Health Organization on March 11, 2020. In response to this global pandemic, we have concentrated our efforts on the health and safety of our employees and patients, while maintaining business continuity and honoring our commitment to deliver life-changing treatments for people battling devastating diseases.

We implemented business continuity plans in March 2020 designed to address the impact and potential impact of COVID-19 on our operations. Effective March 12, 2020, we implemented measures to mitigate the spread of COVID-19 and contribute to the ongoing public health effort to reduce the spread of the virus. We formed a COVID-19 Response Team to maintain business continuity while safeguarding employee and patient health. We also mandated a work-from-home policy for most employees and set up additional processes to work from home effectively, including measures to bolster our cybersecurity. Since early June 2020, we have been able to increase the number of employees working onsite, as well as expand the amount and type of manufacturing and lab-based activities being conducted onsite.

Our manufacturing operations and lab-based activities continue with social-distancing and updated protocols for accessing our facilities. As a biopharmaceutical research and development company, we are deemed to provide essential services under the "stay at home" advisory that was issued by the Governor of Massachusetts on March 23, 2020. While we continue to conduct R&D activities, including our ongoing clinical trials, the COVID-19 pandemic has impacted, and may continue to impact, certain of our early-stage discovery efforts and clinical trials. We are working with our clinical investigators, R&D vendors, and supply chain vendors to continually assess and take steps to mitigate the potential impact of COVID-19 on our manufacturing operations and R&D activities.

We will continue to closely monitor the COVID-19 situation (along with emerging or future variants of COVID-19) as we evolve our business continuity plans. Given the global economic slowdown and the other risks and uncertainties associated with COVID-19, our business, financial condition, results of operations, and prospects could be materially adversely affected. For additional information, see "Item 1A. Risk Factors" of this Annual Report on Form 10-K.

Overview

We are a clinical-stage genetic medicines company committed to delivering life-changing treatments for people battling devastating diseases. Using PRISM™, our proprietary discovery and drug development platform that enables the precise design, optimization and production of novel stereopure oligonucleotides, we aspire to develop best in class medicines for genetically defined diseases with a high degree of unmet need.

We are developing oligonucleotides that target ribonucleic acid ("RNA") to either reduce the expression of disease-promoting proteins or transform the production of dysfunctional mutant proteins into the production of functional proteins. By intervening at the RNA level, we have the potential to address diseases that have historically been difficult to treat with small molecules or biologics, while retaining the ability to titrate dose and avoid permanent off-target genetic changes and other challenges associated with DNA editing or gene therapy approaches. The mechanisms that we are currently using to target RNA with our oligonucleotides include silencing, splicing, and ADAR (adenosine deaminases acting on RNA)-mediated RNA editing ("ADAR editing"). Oligonucleotides have additional advantages as a therapeutic class including the ability to access multiple tissue types and the ability to modulate the frequency of dosing to ensure broad distribution within tissues over time. Oligonucleotides also have well-established manufacturing processes and validated test methods based on decades of improvements.

The oligonucleotides we are developing with PRISM are stereopure and differ from the mixture-based oligonucleotides currently on the market or in development by others. A stereopure oligonucleotide is comprised of molecules with atoms precisely arranged in three-dimensional orientations at each linkage. Based on our preclinical studies, we believe that controlling the stereochemistry of each backbone position will allow us to optimize the pharmacological profile of our oligonucleotides by maximizing the potential therapeutic benefit while minimizing the potential for side effects and safety risks. To further mitigate pharmacological risks and potential manufacturing challenges, our approach focuses on designing oligonucleotides without the need for delivery vehicles. Through our work in developing stereopure oligonucleotides, we have created and continue to evolve PRISM, our proprietary discovery and drug development platform.

PRISM enables us to target genetically defined diseases with stereopure oligonucleotides across multiple therapeutic modalities. PRISM combines our unique ability to construct stereopure oligonucleotides with a deep understanding of how the interplay among oligonucleotide sequence, chemistry and backbone stereochemistry impacts key pharmacological properties. By exploring these interactions through iterative analysis of *in vitro* and *in vivo* outcomes and machine learning-driven predictive modeling, we continue to define design principles that we deploy across programs to rapidly develop and manufacture clinical candidates that meet pre-defined product profiles. In August 2020, we introduced our novel PN backbone chemistry modifications, which were discovered through PRISM and have been shown preclinically to increase potency, tissue exposure and durability across various modalities.

Our lead clinical development programs are focused on genetic diseases within neurology. Our first stereopure therapeutic candidates in development, WVE-120101 and WVE-120102, are designed to selectively target mutant huntingtin ("mHTT") and spare wild-type, or healthy, huntingtin ("wtHTT") for the treatment of Huntington's disease ("HD"). WVE-120101 and WVE-120102 are currently being studied in two Phase 1b/2a clinical trials, PRECISION-HD1 and PRECISION-HD2, and we expect to deliver data from both trials at the end of the first quarter of 2021. We also expect to initiate dosing in three new clinical trials with compounds containing our novel PN backbone chemistry modifications in 2021. These new programs include WVE-003, our mHTT SNP3 program for the treatment of HD, WVE-004, our C9orf72 program for the treatment of amyotrophic lateral sclerosis ("ALS") and frontotemporal dementia ("FTD"), and WVE-N531, our Exon 53 program for the treatment of Duchenne muscular dystrophy ("DMD"). We continue to advance our ATXN3 program in SCA3. We are also pursuing additional programs in disorders of the central nervous system ("CNS"), including Alzheimer's disease, Parkinson's disease, and others, in collaboration with Takeda Pharmaceutical Company Limited ("Takeda"). In addition to neurology, our pipeline includes programs in hepatic diseases, including alpha-1 antitrypsin disease ("AATD"), and ophthalmologic disorders, specifically inherited retinal diseases. We continue to invest in PRISM to continue to evolve and apply the expanding capabilities and promise of our unique platform. We have also established and continue to enhance our internal current good manufacturing practices ("cGMP") manufacturing capabilities to increase control and visibility of our drug substance supply chain, while continuing to innovate oligonucleotide manufacturing.

Financial Operations Overview

We have never been profitable, and since our inception, we have incurred significant operating losses. Our net loss was $149.9 million in 2020 and $193.6 million in 2019. As of December 31, 2020 and 2019, we had an accumulated deficit of $683.3 million and $533.4 million, respectively. We expect to incur significant expenses and operating losses for the foreseeable future.

Revenue

We have not generated any product revenue since our inception and do not expect to generate any revenue from the sale of products for the foreseeable future. Our revenue during the years ended December 31, 2020 and 2019 represented revenue earned under our two revenue-generating collaboration agreements: the Pfizer Collaboration Agreement (as defined in Note 5 in the notes to the consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K ("Note 5")), which was entered into in May 2016 and ended by its original terms in May 2020, and the Takeda Collaboration Agreement (as defined in Note 5), which became effective in April 2018.

Operating Expenses

Our operating expenses since inception have consisted primarily of research and development expenses and general and administrative expenses.

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for our research activities, including our discovery efforts, and the development of our product candidates, which include:

- compensation-related expenses, including employee salaries, bonuses, share-based compensation expense and other related benefits expenses for personnel in our research and development organization;
- expenses incurred under agreements with third parties, including contract research organizations ("CROs") that conduct research, preclinical and clinical activities on our behalf, as well as contract manufacturing organizations ("CMOs") that manufacture drug product for use in our preclinical studies and clinical trials;
- expenses incurred related to our internal manufacturing of drug substance for use in our preclinical studies and clinical trials;
- expenses related to compliance with regulatory requirements;
- expenses related to third-party consultants;
- research and development supplies and services expenses; and
- facility-related expenses, including rent, maintenance and other general operating expenses.

We recognize research and development costs as incurred. We recognize external development costs based on an evaluation of the progress to completion of specific tasks using information provided to us by our vendors. Payments for these activities are based on the terms of the individual agreements, which may differ from the pattern of costs incurred, and are reflected in our financial statements as prepaid or accrued expenses.

Our primary research and development focus since inception has been the development of our proprietary discovery and drug development platform, PRISM. We are using PRISM, which includes our novel PN backbone chemistry modifications, to design, develop and commercialize a broad pipeline of nucleic acid therapeutic candidates that target RNA using silencing, splicing, and ADAR editing.

Our research and development expenses consist primarily of expenses related to our CROs, CMOs, consultants, other external vendors and fees paid to global regulatory agencies to conduct our clinical trials, in addition to compensation-related expenses, internal manufacturing expenses, facility-related expenses and other general operating expenses. These expenses are incurred in connection with research and development efforts and our preclinical studies and clinical trials. We track certain external expenses on a program-by-program basis. However, we do not allocate compensation-related expenses, internal manufacturing expenses, equipment repairs and maintenance expense, facility-related expenses or other operating expenses to specific programs. These expenses, which are not allocated on a program-by-program basis, are included in the "PRISM and other research and development expenses" category along with other external expenses related to our discovery and development programs, as well as platform development and identification of potential drug discovery candidates.

The table below summarizes our research and development expenses incurred for the years ended December 31, 2020 and 2019.

	For the Year Ended December 31,	
	2020	2019
	(in thousands)	
DMD programs	$ 7,120	$ 52,793
HD programs	31,325	18,647
ALS and FTD programs	7,908	2,873
PRISM and other research and development expenses (1)	84,591	101,118
Total research and development expenses	$ 130,944	$ 175,431

(1) Includes discovery and development programs, identification of potential drug discovery candidates, compensation-related expenses, internal manufacturing expenses, equipment repairs and maintenance expense, facility-related expenses and other operating expenses, which are not allocated to specific programs.

Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect to continue to incur significant research and development expenses in the foreseeable future as we continue to manage our existing clinical trials, initiate additional clinical trials for certain product candidates, pursue later stages of clinical development for certain product candidates, maintain our manufacturing capabilities and continue to discover and develop additional product candidates in multiple therapeutic areas.

General and Administrative Expenses

General and administrative expenses consist primarily of compensation-related expenses, including salaries, bonuses, share-based compensation and other related benefits costs for personnel in our executive, finance, corporate, legal and administrative functions, as well as compensation-related expenses for our board of directors. General and administrative expenses also include legal fees; expenses associated with being a public company; professional fees for accounting, auditing, tax and consulting services; insurance costs; travel expenses; other operating costs; and facility-related expenses.

Other Income, Net

Other income, net consists primarily of refundable tax credits from tax authorities and dividend and interest income earned on cash and cash equivalents balances for the years ended December 31, 2020 and 2019. We recognize refundable tax credits when there is reasonable assurance that we will comply with the requirements of the refundable tax credit and that the refundable tax credit will be received.

Income Taxes

We are a Singapore multi-national company subject to taxation in the United States and various other jurisdictions.

In 2020, we recorded an income tax benefit of $0.8 million and in 2019 we recorded no income tax benefit or provision. As of December 31, 2020 and 2019, we have recorded a full valuation allowance against our net operating loss carryforwards and federal and state tax credits in all jurisdictions due to uncertainty regarding future taxable income.

Results of Operations

In this section, we discuss the results of our operations for the year ended December 31, 2020 compared to the year ended December 31, 2019.

Comparison of the Year Ended December 31, 2020 to the Year Ended December 31, 2019

The following table summarizes our results of operations for 2020 and 2019:

	For the Year Ended December 31,		
	2020	2019	Change
	(in thousands)		
Revenue	$ 20,077	$ 15,983	$ 4,094
Operating expenses:			
Research and development	130,944	175,431	(44,487)
General and administrative	42,510	48,869	(6,359)
Total operating expenses	173,454	224,300	(50,846)
Loss from operations	(153,377)	(208,317)	54,940
Total other income, net	2,626	14,679	(12,053)
Loss before income taxes	(150,751)	(193,638)	42,887
Income tax benefit (provision), net	841	—	841
Net loss	$ (149,910)	$ (193,638)	$ 43,728

Revenue

Revenue of $20.1 million and $16.0 million was earned under the Pfizer Collaboration Agreement and Takeda Collaboration Agreement for the years ended December 31, 2020 and 2019, respectively. The $4.1 million increase in revenue is primarily due to an increase in research and development services under the Takeda Collaboration Agreement, partially offset by a decrease in research and development services under the Pfizer Collaboration Agreement, which ended by its original terms in May 2020.

Research and Development Expenses

The following table summarizes our research and development expenses incurred for the years ended December 31, 2020 and 2019:

	For the Year Ended December 31,		
	2020	2019	Change
	(in thousands)		
DMD programs	$ 7,120	$ 52,793	$ (45,673)
HD programs	31,325	18,647	12,678
ALS and FTD programs	7,908	2,873	5,035
PRISM and other research and development expenses (1)	84,591	101,118	(16,527)
Total research and development expenses	$ 130,944	$ 175,431	$ (44,487)

(1) Includes discovery and development programs, identification of potential drug discovery candidates, and compensation-related expenses, internal manufacturing expenses, equipment repairs and maintenance expense, facility-related expenses and other operating expenses, which are not allocated to specific programs.

Research and development expenses were $130.9 million for the year ended December 31, 2020, compared to $175.4 million for the year ended December 31, 2019. The decrease of $44.5 million was due primarily to the following:

- a decrease of $45.7 million in external expenses related to our DMD programs, including suvodirsen, due to our December 2019 decision to discontinue the suvodirsen program;
- an increase of $12.7 million in external expenses related to our HD programs, including costs related to our Phase 1b/2a clinical trials, PRECISION-HD1 and PRECISION-HD2, and our PN backbone containing WVE-003 program;
- an increase of $5.0 million in external expenses related to our ALS and FTD programs, including our PN backbone containing WVE-004 program; and
- a decrease of $16.5 million in internal and external research and development expenses that are not allocated on a program-by-program basis and are related to other discovery and development programs, including PRISM and the identification of potential drug discovery candidates, primarily due to decreases in supplies, services and compensation-related expenses, due to the February 2020 cost reduction plan.

General and Administrative Expenses

General and administrative expenses were $42.5 million for the year ended December 31, 2020 compared to $48.9 million for the year ended December 31, 2019. The decrease of $6.4 million was mainly driven by decreases in supplies and services and compensation-related expenses, due to the February 2020 cost reduction plan.

Other Income, Net

Other income, net for the years ended December 31, 2020 and 2019 was $2.6 million and $14.7 million, respectively. The decrease of approximately $12.1 million in other income, net is mainly related to the $7.7 million decrease in the other income, which was primarily related to the decrease in estimated refundable tax credit due to a decrease in the year-over-year underlying research and development expenses, as well as a $4.3 million decrease in dividend income earned on cash equivalents during the year ended December 31, 2020.

Income Tax Benefit (Provision), Net

During the year ended December 31, 2020, we recorded an income tax benefit of $0.8 million primarily due to the release of a portion of our uncertain tax positions as a result of a lapse in the statute of limitations. During the year ended December 31, 2019 we recorded no income tax benefit or provision.

Liquidity and Capital Resources

Since our inception, we have not generated any product revenue and have incurred recurring net losses. To date, we have primarily funded our operations through private placements of debt and equity securities, public offerings of our ordinary shares and collaborations with third parties. Through December 31, 2020, we have received an aggregate of approximately $808.6 million in net proceeds from these transactions. We received $89.3 million in net proceeds from private placements of our debt and equity securities, $100.4 million in net proceeds from our initial public offering, $40.0 million under the Pfizer Agreements (as defined in Note 5), including $10.0 million as an upfront payment under the Pfizer Collaboration Agreement and $30.0 million in the form of an equity investment, $93.5 million in net proceeds from our April 2017 follow-on underwritten public offering, $170.0 million in upfront payments under the Takeda Agreements (as defined in Note 5), including $110.0 million as an upfront payment under the Takeda Collaboration Agreement (as defined in Note 5) and $60.0 million in the form of an equity investment, $161.8 million in net proceeds from our January 2019 follow-on underwritten public offering, $59.9 million in net proceeds from our at-the-market equity program, and $93.7 million in net proceeds from our September 2020 follow-on underwritten public offering.

As of December 31, 2020, we had cash and cash equivalents of $184.5 million, restricted cash of $3.7 million and an accumulated deficit of $683.3 million. Our operating lease commitments as of December 31, 2020 total $43.8 million, of which $6.3 million is related to payments in 2021 and $37.5 million is related to payments beyond 2021.

We expect that our existing cash and cash equivalents will be sufficient to fund our operations for at least the next twelve months. We have based this expectation on assumptions that may prove to be incorrect, and we may use our available capital resources sooner than we currently expect. In addition, we may elect to raise additional funds before we need them if the conditions for raising capital are favorable due to market conditions or strategic considerations, even if we expect we have sufficient funds for our current or future operating plans.

Until we can generate significant revenue from product sales, if ever, we expect to continue to finance our operations through a combination of public or private equity or debt financings or other sources, which may include collaborations with third parties. In May 2019, we filed a shelf registration statement on Form S-3ASR with the SEC pursuant to which we registered for sale an indeterminate amount of any combination of our ordinary shares, debt securities, warrants, rights and/or units from time to time and at prices and on terms that we may determine. Our shelf registration statement on Form S-3ASR also includes a prospectus covering up to an aggregate of $250 million in ordinary shares that we may issue and sell from time to time, through Jefferies LLC acting as our sales agent, pursuant to the open market sales agreement that we entered into with Jefferies LLC in May 2019, as amended in March 2020, for our “at-the-market” equity program. Since we no longer qualify as a “well-known seasoned issuer” at the time of the filing of this Annual Report on Form 10-K, we have amended the shelf registration statement to register for sale up to $500 million of any combination of our ordinary shares, debt securities, warrants, rights and/or units from time to time and at prices and on terms that we may determine, including the $250 million in ordinary shares that we may issue and sell from time to time pursuant to our “at-the-market” equity program. Adequate additional financing may not be available to us on acceptable terms, or at all. Our inability to raise capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy. We will need to generate significant revenue to achieve profitability, and we may never do so.

Cash Flows

The following table summarizes our sources and uses of cash for each of the periods presented:

	For the Year Ended December 31,	
	2020	2019
	(in thousands)	
Net cash used in operating activities	$ (115,982)	$ (188,231)
Net cash used in investing activities	(1,338)	(3,918)
Net cash provided by financing activities	154,538	164,399
Effect of foreign exchange rates on cash	122	114
Net increase (decrease) in cash, cash equivalents and restricted cash	$ 37,340	$ (27,636)

Operating Activities

During 2020, operating activities used $116.0 million of cash, primarily due to our net loss of $149.9 million, offset by non-cash charges of $24.3 million, partially offset by changes in our operating assets and liabilities of $9.6 million. The non-cash charges for 2020 related mainly to share-based compensation expense of $14.3 million and depreciation expense of $8.1 million. The largest changes in operating assets and liabilities were a decrease of $20.0 million in accounts receivable and a decrease of $20.1 million in deferred revenue, primarily related to the Takeda Collaboration Agreement and a $14.1 million decrease in other assets primarily related to receiving the reimbursement of the refundable tax credits.

During 2019, operating activities used $188.2 million of cash, primarily due to our net loss of $193.6 million and changes in our operating assets and liabilities of approximately $23.3 million, offset by non-cash charges of $28.7 million. The non-cash charges for 2019 related mainly to share-based compensation expense of $19.5 million and $7.6 million of depreciation expense.

Investing Activities

During 2020, investing activities used $1.3 million of cash, consisting of purchases of property and equipment.

During 2019, investing activities used $3.9 million of cash, consisting of purchases of property and equipment.

Financing Activities

During 2020, net cash provided by financing activities was $154.5 million, which was mainly due to the $93.7 million in net proceeds from our September 2020 follow-on underwritten public offering and $59.9 million in net proceeds from our at-the-market equity program.

During 2019, net cash provided by financing activities was $164.4 million, which was due to the $161.8 million in net proceeds from our January 2019 follow-on underwritten public offering and approximately $2.6 million in proceeds from the exercise of share options.

Funding Requirements

We expect to continue to incur significant expenses in connection with our ongoing research and development activities and our internal cGMP manufacturing activities. Furthermore, we anticipate that our expenses will continue to vary if and as we:

- continue to conduct our clinical trials evaluating our product candidates in patients;
- conduct research and preclinical development of discovery targets and advance additional programs into clinical development;
- file clinical trial applications with global regulatory agencies and conduct clinical trials for our programs;
- evaluate next steps for our programs in rare, inherited eye diseases;
- make strategic investments in continuing to innovate our research and development platform, PRISM, and in optimizing our manufacturing processes and formulations;
- maintain our manufacturing capabilities through our internal facility and our CMOs;
- maintain our intellectual property portfolio and consider the acquisition of complementary intellectual property;
- seek and obtain regulatory approvals for our product candidates; and
- establish and build capabilities to market, distribute and sell our product candidates.

We may experience delays or encounter issues with any of the above, including but not limited to failed studies, complex results, safety issues or other regulatory challenges.

Because of the numerous risks and uncertainties associated with the development of drug candidates and because the extent to which we may enter into collaborations with third parties for development of product candidates is unknown, we are unable to estimate the amounts of future capital outlays and operating expenses associated with completing the research and development for our therapeutic programs. Our future capital requirements for our therapeutic programs will depend on many factors, including:

- the progress, results and costs of conducting research and continued preclinical and clinical development for our therapeutic programs and future potential pipeline candidates;
- the number and characteristics of product candidates and programs that we pursue;
- the cost of manufacturing clinical supplies of our product candidates;
- whether and to what extent milestone events are achieved under our collaboration with Takeda or any potential future licensee or collaborator;
- the costs, timing and outcome of regulatory review of our product candidates;
- our ability to obtain marketing approval for our product candidates;
- the costs and timing of future commercialization activities, including manufacturing, marketing, sales and distribution, for any of our product candidates for which we receive marketing approval;
- market acceptance of our product candidates, to the extent any are approved for commercial sale, and the revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims;
- the effect of competing technological and market developments; and
- the extent to which we acquire or invest in businesses, products and technologies, including entering into licensing or collaboration arrangements for product candidates.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain marketing approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Our product revenue, if any, will be derived from sales of products that we do not expect to be commercially available for many years, if ever. Accordingly, we will need to obtain substantial additional funds to achieve our business objectives.

Adequate additional funds may not be available to us on acceptable terms when we need them, or at all. We do not currently have any committed external source of funds, except for committed funds and possible future payments from Takeda under the Takeda Collaboration Agreement. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our existing shareholders will be diluted, and the terms may include liquidation or other preferences that adversely affect the rights of our shareholders. Additional debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends and may require the issuance of warrants, which could potentially dilute our shareholders' ownership interests.

If we raise additional funds through collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development programs or any future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Off-Balance Sheet Arrangements

We had one off-balance sheet arrangement (as that term is defined in Item 303(a)(4)(ii) of Regulation S-K) as of December 31, 2020, as we exercised our option in December 2020 to lease the remaining office and laboratory space at our Cambridge, Massachusetts facility. The combined space will constitute the entire building. The lease for the additional space is expected to commence on October 1, 2021 with a term of five years. As the lease term for the additional space has not yet commenced, we have not yet recognized rent expense for the additional space. On the commencement date of the lease for the additional space in 2021, we will record a right-of-use asset and corresponding operating lease liability and begin recognizing straight-line rent expense. We have not made any payments to date related to the lease of the additional space. We expect future cash commitments related to this lease for the additional space to total $5.4 million, of which $0.3 million is related to payments in 2021 and $5.1 million is related to payments beyond 2021.

We had no other off-balance sheet arrangements as of December 31, 2020 that have, or are reasonably likely to have, a current or future effect on our financial condition, changes in financial condition, revenues or expenses, results of operations, liquidity, capital expenditures or capital resources.

Recently Issued and Adopted Accounting Pronouncements

For detailed information regarding recently issued and adopted accounting pronouncements and the expected impact on our consolidated financial statements, see Note 2 "Significant Accounting Policies" in the notes to the consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K.

Critical Accounting Policies and Significant Judgments and Estimates

Our consolidated financial statements are prepared in accordance with generally accepted accounting principles in the United States of America ("U.S. GAAP"). The preparation of our financial statements and related disclosures requires us to make estimates and assumptions that affect the reported amount of assets, liabilities, revenue, costs and expenses and related disclosures. We believe that our revenue recognition policy, particularly (a) assessing the number of performance obligations; (b) determining the transaction price; (c) allocating the transaction price to the performance obligations in the contract; and (d) determining the pattern over which performance obligations are satisfied, including estimates to complete performance obligations, and the assumptions and estimates used in our analysis of contracts with CROs and CMOs to estimate the contract expense, involve a greater degree of judgment, and therefore we consider them to be our critical accounting policies. We evaluate our estimates and assumptions on an ongoing basis. Our actual results may differ from these estimates under different assumptions and conditions.

Revenue Recognition

The Company recognizes revenue in accordance with Accounting Standards Codification ("ASC") Topic 606, Revenue from Contracts with Customers ("ASC 606"). Under this method, the Company revised its consolidated financial statements for the years ended December 31, 2017 and 2016, and applicable interim periods within those years, as if ASC 606 had been effective for those periods. This standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, and financial instruments. Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration that the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs the following five-step analysis: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. The Company only applies the five-step analysis to contracts when it is probable that the entity will collect the consideration to which it is entitled in exchange for the goods or services it transfers to the customer. At contract inception, once the contract is determined to be within the scope of ASC 606, the Company assesses the goods or services promised within each contract, determines those that are performance obligations, and assesses whether each promised good or service is distinct. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

The Company has entered into collaboration agreements for research, development, and commercial services, under which the Company licenses certain rights to its product candidates to third parties. The terms of these arrangements typically include payment to the Company of one or more of the following: non-refundable, upfront license fees; reimbursement of certain costs; customer option exercise fees; development, regulatory and commercial milestone payments; and royalties on net sales of licensed products. Any variable consideration is constrained, and therefore, the cumulative revenue associated with this consideration is not recognized until it is deemed not to be at significant risk of reversal.

In determining the appropriate amount of revenue to be recognized as the Company fulfills its obligations under each of its agreements for which the collaboration partner is also a customer, the Company performs the following steps: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations, including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations; and (v) recognition of revenue when (or as) the Company satisfies each performance obligation. As part of the accounting for these arrangements, the Company must use significant judgment to determine: (a) the number of performance obligations based on the determination under step (ii) above; (b) the transaction price under step (iii) above; and (c) the timing of satisfaction of performance obligations as a measure of progress in step (v) above. The Company uses significant judgment to determine whether milestones or other variable consideration, except for royalties, should be included in the transaction price as described further below. The transaction price is allocated to the optional goods and services the Company expects to provide. The Company uses estimates to determine the timing of satisfaction of performance obligations.

Amounts received prior to being recognized as revenue are recorded as deferred revenue. Amounts expected to be recognized as revenue within the 12 months following the balance sheet date are classified as current portion of deferred revenue in the accompanying consolidated balance sheets. Amounts not expected to be recognized as revenue within the 12 months following the balance sheet date are classified as deferred revenue, net of current portion.

Licenses of intellectual property: In assessing whether a promise or performance obligation is distinct from the other promises, the Company considers factors such as the research, development, manufacturing and commercialization capabilities of the customer and the availability of the associated expertise in the general marketplace. In addition, the Company considers whether the customer can benefit from a promise for its intended purpose without the receipt of the remaining promise, whether the value of the promise is dependent on the unsatisfied promise, whether there are other vendors that could provide the remaining promise, and whether it is separately identifiable from the remaining promise. For licenses that are combined with other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Research and development services: If an arrangement is determined to contain a promise or obligation for the Company to perform research and development services, the Company must determine whether these services are distinct from other promises in the arrangement. In assessing whether the services are distinct from the other promises, the Company considers the capabilities of the customer to perform these same services. In addition, the Company considers whether the customer can benefit from a promise for its intended purpose without the receipt of the remaining promise, whether the value of the promise is dependent on the unsatisfied promise, whether there are other vendors that could provide the remaining promise, and whether it is separately identifiable from the remaining promise. For research and development services that are combined with other promises, the Company utilizes judgment to

assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Customer options: If an arrangement is determined to contain customer options that allow the customer to acquire additional goods or services, the goods and services underlying the customer options are not considered to be performance obligations at the outset of the arrangement, as they are contingent upon option exercise. The Company evaluates the customer options for material rights, that is, the option to acquire additional goods or services for free or at a discount. If the customer options are determined to represent a material right, the material right is recognized as a separate performance obligation at the outset of the arrangement. The Company allocates the transaction price to material rights based on the standalone selling price. As a practical alternative to estimating the standalone selling price when the goods or services are both (i) similar to the original goods and services in the contract and (ii) provided in accordance with the terms of the original contract, the Company allocates the total amount of consideration expected to be received from the customer to the total goods or services expected to be provided to the customer. Amounts allocated to any material right are not recognized as revenue until the option is exercised and the performance obligation is satisfied.

Milestone payments: At the inception of each arrangement that includes milestone payments, the Company evaluates whether a significant reversal of cumulative revenue provided in conjunction with achieving the milestones is probable, and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant reversal of cumulative revenue would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the control of the Company or the licensee, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. For other milestones, the Company evaluates factors such as the scientific, clinical, regulatory, commercial, and other risks that must be overcome to achieve the particular milestone in making this assessment. There is considerable judgment involved in determining whether it is probable that a significant reversal of cumulative revenue would not occur. At the end of each subsequent reporting period, the Company reevaluates the probability of achievement of all milestones subject to constraint and, if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues and earnings in the period of adjustment.

Royalties: For arrangements that include sales-based royalties, including milestone payments based on a level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied). To date, the Company has not recognized any royalty revenue resulting from any of its licensing arrangements.

Contract costs: The Company recognizes as an asset the incremental costs of obtaining a contract with a customer if the costs are expected to be recovered. As a practical expedient, the Company recognizes the incremental costs of obtaining a contract as an expense when incurred if the amortization period of the asset that it otherwise would have recognized is one year or less. To date, the Company has not incurred any incremental costs of obtaining a contract with a customer.

For additional discussion of accounting for collaboration revenues, see Note 5 of our consolidated financial statements.

Prepaid and Accrued Research and Development Expenses

As we prepare our consolidated financial statements, we are required to estimate our prepaid and accrued expenses. For certain contracts with our CROs and CMOs, if the billing terms do not align with the pattern in which the work is completed by the CRO or CMO as of the end of the period, we are required to perform an analysis to estimate the expense, for the period and to date for each contract.

Contracts that are subject to this analysis generally relate to the following services: research and development services, manufacturing services, toxicology studies and clinical trial services. Once we have completed our analysis, we will record the estimated expense in the period for each contract and, depending on the invoicing activity related to each contract, we either have a prepaid or accrual as of the end of the period. We base our estimates on communications with internal study managers, our knowledge of the ongoing and past work at the CROs and CMOs, and communications and reporting from our CROs and CMOs, where applicable.

Refundable Tax Credits

Refundable tax credits from certain governmental bodies are presented within other income, net. Other income, net related to the refundable tax credits is recognized when it is probable that we have complied with any attached conditions and will receive the reimbursement. Management is required to develop estimates at each reporting date on the amount of the refundable tax credits, which includes an estimate of qualifying expenditure. Although, we do not expect our estimates to be materially different from amounts claimed and subsequently reimbursed, if our estimates of the qualifying expenditure differ from the amount claimed, we may report amounts that are too high or too low in any particular period.

Item 7A. Quantitative and Qualitative Disclosures about Market Risk

Market risk represents the risk of loss that may impact our financial position due to adverse changes in financial market prices and rates. Our market risk exposure is primarily the result of fluctuations in interest rates and foreign exchange rates as well as, to a lesser extent, inflation and capital market risk.

Interest Rate Risk

We are exposed to interest rate risk in the ordinary course of our business. Our cash and cash equivalents are held in readily available checking and money market accounts.

Foreign Currency Risk

Due to our operations outside of the Unites States, we are exposed to market risk related to changes in foreign currency exchange rates. Historically, we have not hedged our foreign currency exposure. Changes in the relative values of currencies occur regularly and, in some instances, could materially adversely affect our business, our financial condition, the results of our operations or our cash flows. For the years ended December 31, 2020 and 2019, changes in foreign currency exchange rates did not have a material impact on our historical financial position, our business, our financial condition, the results of our operations or our cash flows.

A hypothetical 10% change in foreign currency rates would not have a material impact on our historical financial position or results of operations. However, there can be no assurance that changes in foreign currency exchange rates will not have a material adverse impact on us in the future.

Inflation Risk

We do not believe that inflation had a material effect on our business, financial condition or results of operations in the last three years.

Capital Market Risk

We currently have no product revenues and depend on funds raised through other sources. One possible source of funding is through further equity offerings. Our ability to raise funds in this manner depends upon capital market forces affecting our share price.

Item 8. Financial Statements and Supplementary Data

The information required by this Item 8 is included at the end of this Annual Report on Form 10-K beginning on page F-1.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure

Not applicable.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our principal executive officer and principal financial officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2020. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to its management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2020, our principal executive officer and principal financial officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting identified in connection with the evaluation of such internal control required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the fiscal quarter ended December 31, 2020 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Management's Annual Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) under the Securities Exchange Act of 1934, as amended, as a process designed by, or under the supervision of, the company's principal executive and principal financial officers and effected by the company's board of directors, management and other personnel to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles and includes those policies and procedures that:

- Pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company;
- Provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures are being made only in accordance with authorizations of management and directors of the company; and
- Provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of the company's assets that could have a material effect on the financial statements.

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

Our management assessed the effectiveness of our internal control over financial reporting as of December 31, 2020. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission ("COSO") in Internal Control-Integrated Framework (2013).

Based on our assessment, management believes that, as of December 31, 2020, our internal control over financial reporting is effective based on those criteria.

As a "smaller reporting company" and a "non-accelerated filer," we are exempt from the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002. As a result, KPMG LLP, our independent registered public accounting firm, has not audited or issued an attestation report with respect to the effectiveness of our internal control over financial reporting as of December 31, 2020.

Item 9B. Other Information

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

Information required by this item will be contained in our definitive proxy statement to be filed with the Securities and Exchange Commission on Schedule 14A in connection with our 2021 Annual General Meeting of Shareholders, or the Proxy Statement, if the Proxy Statement is filed not later than 120 days after the end of our fiscal year ended December 31, 2020, in the sections titled “Management and Corporate Governance,” “Delinquent Section 16(a) Reports,” and “Code of Business Conduct and Ethics,” and is incorporated herein by reference. If the Proxy Statement is not filed within such 120-day period, the information required by this item will be contained in an amendment to this Annual Report on Form 10-K to be filed with the Securities and Exchange Commission, or the Form 10-K/A.

Item 11. Executive Compensation

The information required by this item is incorporated by reference to the information set forth in the section titled “Executive Officer and Director Compensation” in our Proxy Statement. If the Proxy Statement is not filed within 120 days after the end of our fiscal year ended December 31, 2020, the information required by this item will be contained in the Form 10-K/A.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters

The information required by this item is incorporated by reference to the information set forth in the sections titled “Security Ownership of Certain Beneficial Owners and Management” and “Equity Compensation Plan Information” in our Proxy Statement. If the Proxy Statement is not filed within 120 days after the end of our fiscal year ended December 31, 2020, the information required by this item will be contained in the Form 10-K/A.

Item 13. Certain Relationships and Related Transactions, and Director Independence

The information required by this item is incorporated by reference to the information set forth in the sections titled “Certain Relationships and Related Person Transactions” and “Management and Corporate Governance – Board of Directors” in our Proxy Statement. If the Proxy Statement is not filed within 120 days after the end of our fiscal year ended December 31, 2020, the information required by this item will be contained in the Form 10-K/A.

Item 14. Principal Accountant Fees and Services

The information required by this item regarding principal accountant fees and services is incorporated by reference to the information set forth in the sections titled “Principal Accountant Fees and Services” and “Policy on Audit Committee Pre-Approval of Audit and Permissible Non-Audit Services of Independent Public Accountant and Independent Singapore Auditor” in our Proxy Statement. If the Proxy Statement is not filed within 120 days after the end of our fiscal year ended December 31, 2020, the information required by this item will be contained in the Form 10-K/A.

PART IV

Item 15. Exhibits and Financial Statement Schedules

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

1. Financial Statements

See Index to Consolidated Financial Statements on page 104 of this Annual Report on Form 10-K.

2. Financial Statement Schedules

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

3. Exhibits

The following is a list of exhibits filed as part of this Annual Report on Form 10-K.

Exhibit Number	Exhibit Description	Filed with this Report	Incorporated by Reference herein from Form or Schedule	Filing Date	SEC File/Reg. Number
3.1	Constitution (formerly known as Memorandum of Association and Articles of Association)		Amendment No. 5 to Form S-1 (Exhibit 3.2)	11/10/2015	333-207379
4.1	Form of Specimen Ordinary Share Certificate		Amendment No. 3 to Form S-1 (Exhibit 4.1)	11/06/2015	333-207379
4.2	Description of Securities of the Registrant and Comparison of Shareholder Rights	X			
4.3.1	Investors' Rights Agreement by and among the Registrant and certain of its shareholders, dated as of August 14, 2015		Form S-1 (Exhibit 4.2)	10/09/2015	333-207379
4.3.2	Amendment No. 1 to Investors' Rights Agreement by and among the Registrant and certain of its shareholders, dated as of November 8, 2018		Form 10-Q (Exhibit 10.2)	11/09/2018	001-37627
4.4	Share Purchase Agreement by and between the Registrant and C.P. Pharmaceuticals International C.V., dated as of May 5, 2016		Form 10-Q (Exhibit 10.2)	08/15/2016	001-37627
Lease Agreements					
10.1	Lease Agreement by and among Harvard Real Estate—Allston, Inc., Shin Nippon Biomedical Laboratories Ltd., dated June 25, 2009		Form S-1 (Exhibit 10.2)	10/09/2015	333-207379
10.2	Commercial Lease Agreement by and among SNBL USA, Ltd. and Ontorii, Inc. (now Wave Life Sciences USA, Inc.), dated as of January 1, 2010		Form S-1 (Exhibit 10.4)	10/09/2015	333-207379
10.3	Consent to Office Space Sublease by and among SNBL USA, Ltd, Ontorii, Inc. (now Wave Life Sciences USA, Inc.) and Harvard Real Estate—Allston, Inc., dated as of January 1, 2010		Form S-1 (Exhibit 10.3)	10/09/2015	333-207379
10.4	Amendment 1 to the Commercial Lease Agreement by and between SNBL USA, Ltd. and Ontorii, Inc. (now Wave Life Sciences USA, Inc.), dated as of July 1, 2011		Form S-1 (Exhibit 10.5)	10/09/2015	333-207379

Exhibit Number	Exhibit Description	Filed with this Report	Incorporated by Reference herein from Form or Schedule	Filing Date	SEC File/Reg. Number
10.5.1	Lease Agreement by and between the Wave Life Sciences USA, Inc. the Registrant and King 733 Concord LLC, dated as of April 6, 2015		Form S-1 (Exhibit 10.7)	10/09/2015	333-207379
10.5.2	First Amendment (to Lease) by and between Wave Life Sciences USA, Inc. and CPI/King 733 Concord Owner, LLC, dated as of December 9, 2020	X			
10.6.1	Lease Agreement by and between Wave Life Sciences USA, Inc. and King 115 Hartwell LLC, dated as of September 26, 2016.		Form 8-K (Exhibit 10.1)	01/06/2017	001-37627
10.6.2	First Amendment (to Lease) by and between Wave Life Sciences USA, Inc. and King 115 Hartwell LLC, dated as of December 31, 2016		Form 8-K (Exhibit 10.1)	01/06/2017	001-37627
Collaboration and License Agreements					
10.7†	Collaboration and License Agreement by and between Wave Life Sciences USA, Inc., Wave Life Sciences UK Limited and Takeda Pharmaceutical Company Limited, dated as of February 19, 2018		Form 10-Q (Exhibit 10.1)	05/09/2018	001-37627
10.8	Share Purchase Agreement by and between Takeda Pharmaceutical Company Limited and the Registrant, dated as of February 19, 2018		Form 10-Q (Exhibit 10.2)	05/09/2018	001-37627
10.9	Investor Agreement by and between Takeda Pharmaceutical Company Limited and the Registrant, dated as of April 2, 2018		Form 10-Q (Exhibit 10.3)	05/09/2018	001-37627
Agreements with Executive Officers and Directors					
10.10+	Form of Deed of Indemnity by and between the Registrant and each of its directors and certain of its officers		Form S-1 (Exhibit 10.11)	10/09/2015	333-207379
10.11+	Employment Agreement, as amended and restated, between the Registrant and Paul B. Bolno, dated as of May 8, 2020		Form 10-Q (Exhibit 10.1)	08/10/2020	333-207379
10.12+	Employment Agreement, as amended and restated, between the Registrant and Chandra Vargeese, dated as of May 8, 2020		Form 10-Q (Exhibit 10.2)	08/10/2020	333-207379
10.13+	Offer Letter by and between the Registrant and Christopher Francis, Ph.D., dated as of March 10, 2014		Form S-1 (Exhibit 10.15)	10/09/2015	333-207379
10.14+	Employment Agreement between the Registrant and Michael Panzara, M.D. dated as of July 11, 2016		Form 10-Q (Exhibit 10.4)	11/09/2016	001-37627
10.15+	Employment Agreement, as amended and restated, between the Registrant and Kyle Moran, dated as of January 1, 2021	X			

Exhibit Number	Exhibit Description	Filed with this Report	Incorporated by Reference herein from Form or Schedule	Filing Date	SEC File/Reg. Number
10.16+	Non-Employee Director Compensation Policy, as amended, effective as of August 18, 2020		Form 10-Q (Exhibit 10.1)	11/09/2020	001-37627
10.17+	Consulting Agreement by and between Ontorii, Inc. (now Wave Life Sciences USA, Inc.) and Gregory Verdine, dated as of April 1, 2012		Form S-1 (Exhibit 10.16)	10/09/2015	333-207379
10.18+	Nominee Director Fee Agreement by and between the Registrant and Miura & Associates Management Consultants Pte. Ltd., dated as of October 23, 2012		Form S-1 (Exhibit 10.17)	10/09/2015	333-207379
Equity and Other Compensation Plans					
10.19+	Wave Life Sciences Ltd. 2014 Equity Incentive Plan, as amended (the "2014 Equity Plan")		Form 10-Q (Exhibit 10.1)	11/09/2017	001-37627
10.20+	Wave Life Sciences Ltd. 2019 Employee Share Purchase Plan, effective as of August 15, 2019		Form 10-Q (Exhibit 10.1)	11/05/2019	001-37627
10.21.1+	Form of Non-qualified Share Option Agreement under the 2014 Equity Plan, effective as of September 20, 2016		Form 10-Q (Exhibit 10.2)	11/09/2017	001-37627
10.21.2+	Form of Non-qualified Share Option Agreement under the 2014 Equity Plan, effective as of January 1, 2018		Form 10-K (Exhibit 10.23.3)	03/01/2019	001-37627
10.22.1+	Form of Incentive Share Option Agreement under the 2014 Equity Plan, effective as of December 2014		Form S-8 (Exhibit 10.1)	12/17/2015	333-208598
10.22.2+	Form of Incentive Share Option Agreement under the 2014 Equity Plan, effective as of September 20, 2016		Form 10-Q (Exhibit 10.3)	11/09/2017	001-37627
10.23.1+	Form of Restricted Share Unit Agreement under the 2014 Equity Plan, effective as of June 16, 2016		Form 10-Q (Exhibit 10.4)	11/09/2017	001-37627
10.23.2+	Form of Restricted Share Unit Agreement under the 2014 Equity Plan, effective as of January 1, 2018		Form 10-K (Exhibit 10.25.2)	03/01/2019	001-37627
10.23.3+	Form of Restricted Share Unit Agreement under the 2014 Equity Incentive Plan, effective as of January 1, 2019		Form 10-Q (Exhibit 10.1)	05/10/2019	001-37627
10.23.4+	Form of Performance-Based Restricted Share Unit Agreement under the 2014 Equity Incentive Plan, effective as of March 7, 2019		Form 10-Q (Exhibit 10.2)	05/10/2019	001-37627
10.24.1+	Form of Non-qualified Share Option Agreement for UK Participants under the 2014 Equity Plan, effective as of June 21, 2017		Form 10-Q (Exhibit 10.5)	11/09/2017	001-37627
10.24.2+	Form of Non-qualified Share Option Agreement for UK Participants under the 2014 Equity Plan, effective as of January 1, 2018		Form 10-K (Exhibit 10.26.2)	03/01/2019	001-37627
10.25	Form of Inducement Non-qualified Share Option Agreement		Form 10-Q (Exhibit 10.3)	08/10/2020	001-37627
10.26.1	Open Market Sale Agreement, dated as of May 10, 2019, by and between the Registrant and Jefferies LLC.		Form S-3ASR (Exhibit 1.2)	05/10/2019	333-231382
10.26.2	No. 1 to Open Market Sale Agreement, dated as of March 2, 2020, by and between the Registrant and Jefferies LLC		POSASR (Exhibit 1.3)	03/02/2020	333-231382
21.1	List of Subsidiaries of the Registrant		Form 10-K (Exhibit 21.1)	03/12/2018	001-37627

Exhibit Number	Exhibit Description	Filed with this Report	Incorporated by Reference herein from Form or Schedule	Filing Date	SEC File/Reg. Number
23.1	Consent of Independent Registered Public Accounting Firm	X			
24.1	Power of Attorney (included on signature page to this Annual Report on Form 10-K)	X			
31.1	Certifications of Principal Executive Officer pursuant to Rule 13a-14(a)	X			
31.2	Certifications of Principal Financial Officer pursuant to Rule 13a-14(a)	X			
32*	Certification pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, by Principal Executive Officer and Principal Financial Officer.	X			
101.INS	XBRL Instance Document – The Instance Document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document	X			
101.SCH	Inline XBRL Taxonomy Extension Schema Document	X			
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document	X			
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document	X			
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document	X			
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document	X			
104	The cover page for this Annual Report on Form 10-K for the year ended December 31, 2020 is contained in Exhibit 101 and has been formatted in Inline XBRL.	X			

(*) The certification attached as Exhibit 32 that accompanies this Annual Report on Form 10-K is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of Wave Life Sciences Ltd. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, whether made before or after the date of this Form 10-K, irrespective of any general incorporation language contained in such filing.

(+) Indicates management contract or compensatory plan or arrangement.

(†) Confidential treatment has been granted with respect to certain portions of this exhibit. Omitted portions have been filed separately with the Securities and Exchange Commission.

Item 16. Form 10-K Summary

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, as amended, the Registrant has duly caused this Report to be signed on its behalf by the undersigned, thereunto duly authorized.

Wave Life Sciences Ltd.

Date: March 4, 2021

By: /s/ Paul B. Bolno, M.D.
Paul B. Bolno, M.D.
President and Chief Executive Officer

POWER OF ATTORNEY

Each person whose individual signature appears below hereby authorizes and appoints Paul B. Bolno, M.D. with full power of substitution and resubstitution and full power to act, as his or her true and lawful attorney-in-fact and agent to act in his or her name, place and stead and to execute in the name and on behalf of each person, individually and in each capacity stated below, and to file any and all amendments to this Report and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorney-in-fact and agent, full power and authority to do and perform each and every act and thing, ratifying and confirming all that said attorney-in-fact and agent or his substitute or substitutes may lawfully do or cause to be done by virtue thereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this Report has been signed below by the following persons on behalf of the Registrant in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Paul B. Bolno, M.D. Paul B. Bolno, M.D.	President, Chief Executive Officer and Director (*principal executive officer*)	March 4, 2021
/s/ Kyle Moran Kyle Moran	Chief Financial Officer (*principal financial officer and principal accounting officer*)	March 4, 2021
/s/ Christian Henry Christian Henry	Chairman of the Board of Directors	March 4, 2021
/s/ Gregory L. Verdine, Ph.D. Gregory L. Verdine, Ph.D.	Director	March 4, 2021
/s/ Peter Kolchinsky, Ph.D. Peter Kolchinsky, Ph.D.	Director	March 4, 2021
/s/ Aik-Na Tan Aik-Na Tan	Director	March 4, 2021
/s/ Adrian Rawcliffe Adrian Rawcliffe	Director	March 4, 2021
/s/ Ken Takanashi Ken Takanashi	Director	March 4, 2021
 Mark H. N. Corrigan, M.D.	Director	March 4, 2021
/s/ Heidi L. Wagner Heidi L. Wagner	Director	March 4, 2021

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Shareholders and Board of Directors
Wave Life Sciences Ltd.:

Opinion on the Consolidated Financial Statements

We have audited the accompanying consolidated balance sheets of Wave Life Sciences Ltd. and subsidiaries (the Company) as of December 31, 2020 and 2019, the related consolidated statements of operations and comprehensive loss, Series A preferred shares and shareholders' equity, and cash flows for the years then ended, and the related notes (collectively, the consolidated financial statements). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2020 and 2019, and the results of its operations and its cash flows for the years then ended, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

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

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits, we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

Critical Audit Matter

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

Evaluation of revenue recognition for certain research and development services

As discussed in Notes 2 and 5 to the consolidated financial statements, the Company is party to collaboration agreements which have various obligations, including the requirement to provide research and development (R&D) services. The Company recognizes R&D services revenue over time based on a measure of proportional performance using estimated costs or hours. Amounts received by the Company in advance of performance are recorded as a deferred revenue. For the year ended December 31, 2020, the Company recognized revenue of $20,077 thousand, which related to R&D services performed. In addition, as of December 31, 2020, a portion of the Company's current and long-term deferred revenue relates to R&D services.

We identified the evaluation of revenue recognition for certain R&D services as a critical audit matter. Specifically, the estimate of costs to be incurred in satisfying R&D performance obligations was subjective and required significant auditor judgment. Evaluating the estimated effort required to complete R&D services, including the assessment of the nature and complexity of the work to be performed, involved a high degree of auditor judgment.

The following are the primary procedures we performed to address this critical audit matter. We evaluated the design and implementation of certain internal controls over the Company's estimation of the costs to be incurred in satisfying certain R&D performance obligations. We selected certain R&D performance obligations and read the underlying contract with the customer, evaluated the determination of the method for measuring progress, and tested the Company's estimate of total contract costs to be incurred by (1) comparing the Company's prior period estimates to subsequent actual experience to assess the Company's ability to estimate accurately and (2) corroborating the estimate of remaining costs to be incurred made by financial management with R&D personnel of the Company.

/s/ KPMG LLP

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

Boston, Massachusetts
March 4, 2021

WAVE LIFE SCIENCES LTD.
CONSOLIDATED BALANCE SHEETS

(In thousands, except share amounts)

	December 31, 2020	December 31, 2019
Assets		
Current assets:		
Cash and cash equivalents	$ 184,497	$ 147,161
Current portion of accounts receivable	30,000	20,000
Prepaid expenses	10,434	9,626
Other current assets	5,111	8,689
Total current assets	230,042	185,476
Long-term assets:		
Accounts receivable, net of current portion	—	30,000
Property and equipment, net	29,198	36,368
Operating lease right-of-use assets	16,232	18,101
Restricted cash	3,651	3,647
Other assets	115	10,658
Total long-term assets	49,196	98,774
Total assets	$ 279,238	$ 284,250
Liabilities, Series A preferred shares and shareholders' equity		
Current liabilities:		
Accounts payable	$ 13,795	$ 9,073
Accrued expenses and other current liabilities	11,971	16,185
Current portion of deferred revenue	91,560	89,652
Current portion of operating lease liability	3,714	3,243
Total current liabilities	121,040	118,153
Long-term liabilities:		
Deferred revenue, net of current portion	41,481	63,466
Operating lease liability, net of current portion	25,591	29,304
Other liabilities	474	1,721
Total long-term liabilities	67,546	94,491
Total liabilities	$ 188,586	$ 212,644
Series A preferred shares, no par value; 3,901,348 shares issued and outstanding at December 31, 2020 and 2019	$ 7,874	$ 7,874
Shareholders' equity:		
Ordinary shares, no par value; 48,778,678 and 34,340,690 shares issued and outstanding at December 31, 2020 and 2019, respectively	694,085	539,547
Additional paid-in capital	71,573	57,277
Accumulated other comprehensive income	389	267
Accumulated deficit	(683,269)	(533,359)
Total shareholders' equity	82,778	63,732
Total liabilities, Series A preferred shares and shareholders' equity	$ 279,238	$ 284,250

The accompanying notes are an integral part of the consolidated financial statements.

WAVE LIFE SCIENCES LTD.
CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS

(In thousands, except share and per share amounts)

	For the Year Ended December 31,	
	2020	2019
Revenue	$ 20,077	$ 15,983
Operating expenses:		
Research and development	130,944	175,431
General and administrative	42,510	48,869
Total operating expenses	173,454	224,300
Loss from operations	(153,377)	(208,317)
Other income, net:		
Dividend income	584	4,912
Interest income (expense), net	(16)	29
Other income, net	2,058	9,738
Total other income, net	2,626	14,679
Loss before income taxes	(150,751)	(193,638)
Income tax benefit (provision), net	841	—
Net loss	$ (149,910)	$ (193,638)
Net loss per share attributable to ordinary shareholders—basic and diluted	$ (3.82)	$ (5.72)
Weighted-average ordinary shares used in computing net loss per share attributable to ordinary shareholders—basic and diluted	39,227,618	33,866,487
Other comprehensive income (loss):		
Net loss	$ (149,910)	$ (193,638)
Foreign currency translation	122	114
Comprehensive loss	(149,788)	(193,524)

The accompanying notes are an integral part of the consolidated financial statements.

WAVE LIFE SCIENCES LTD.
CONSOLIDATED STATEMENTS OF SERIES A PREFERRED SHARES AND SHAREHOLDERS' EQUITY

(In thousands, except share amounts)

	Series A Preferred Shares		Ordinary Shares		Additional Paid-In-Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Shareholders' Equity
	Shares	Amount	Shares	Amount				
Balance at December 31, 2018	3,901,348	$ 7,874	29,472,197	$ 375,148	$ 37,768	$ 153	$ (339,721)	$ 73,348
Issuance of ordinary shares	—	—	4,542,500	161,792	—	—	—	161,792
Share-based compensation	—	—	—	—	19,509	—	—	19,509
Vesting of RSUs	—	—	112,437	—	—	—	—	—
Option exercises	—	—	213,556	2,607	—	—	—	2,607
Other comprehensive income	—	—	—	—	—	114	—	114
Net loss	—	—	—	—	—	—	(193,638)	(193,638)
Balance at December 31, 2019	3,901,348	$ 7,874	34,340,690	$ 539,547	$ 57,277	$ 267	$ (533,359)	$ 63,732
Issuance of ordinary shares, net of offering costs	—	—	8,333,334	93,744	—	—	—	93,744
Issuance of ordinary shares pursuant to the at-the-market equity program, net			5,583,022	59,882	—	—	—	59,882
Share-based compensation	—	—	—	—	14,296	—	—	14,296
Vesting of RSUs	—	—	208,123	—	—	—	—	—
Option exercises	—	—	288,270	741	—	—	—	741
Issuance of ordinary shares under the ESPP			25,239	171	—	—	—	171
Other comprehensive income	—	—	—	—	—	122	—	122
Net loss	—	—	—	—	—	—	(149,910)	(149,910)
Balance at December 31, 2020	3,901,348	$ 7,874	48,778,678	$ 694,085	$ 71,573	$ 389	$ (683,269)	$ 82,778

The accompanying notes are an integral part of the consolidated financial statements.

WAVE LIFE SCIENCES LTD.
CONSOLIDATED STATEMENTS OF CASH FLOWS

(In thousands)

	For the Year Ended December 31,	
	2020	**2019**
Cash flows from operating activities		
Net loss	$ (149,910)	$ (193,638)
Adjustments to reconcile net loss to net cash used in operating activities:		
Amortization of right-of-use assets	1,869	1,613
Depreciation of property and equipment	8,114	7,588
Share-based compensation expense	14,296	19,509
Changes in operating assets and liabilities:		
Accounts receivable	20,000	10,000
Prepaid expenses	(808)	(3,665)
Other assets	14,121	(8,369)
Accounts payable	5,117	(3,497)
Accrued expenses and other current liabilities	(4,214)	1,448
Deferred revenue	(20,077)	(15,983)
Operating lease liabilities	(3,243)	(2,816)
Other non-current liabilities	(1,247)	(421)
Net cash used in operating activities	(115,982)	(188,231)
Cash flows from investing activities		
Purchases of property and equipment	(1,338)	(3,918)
Net cash used in investing activities	(1,338)	(3,918)
Cash flows from financing activities		
Proceeds from issuance of ordinary shares, net of offering costs	93,744	161,792
Proceeds from issuance of ordinary shares pursuant to the at-the-market equity program, net	59,882	—
Proceeds from the exercise of share options	741	2,607
Proceeds from the employee share purchase program	171	—
Net cash provided by financing activities	154,538	164,399
Effect of foreign exchange rates on cash	122	114
Net increase (decrease) in cash, cash equivalents and restricted cash	37,340	(27,636)
Cash, cash equivalents and restricted cash, beginning of period	150,808	178,444
Cash, cash equivalents and restricted cash, end of period	$ 188,148	$ 150,808

The accompanying notes are an integral part of the consolidated financial statements.

1. THE COMPANY

Organization

Wave Life Sciences Ltd. (together with its subsidiaries, "Wave" or the "Company") is a clinical-stage genetic medicines company committed to delivering life-changing treatments for people battling devastating diseases. PRISM, Wave's proprietary discovery and drug development platform, enables Wave to target genetically defined diseases with stereopure oligonucleotides across multiple therapeutic modalities.

The Company was incorporated in Singapore on July 23, 2012 and has its principal U.S. office in Cambridge, Massachusetts. The Company was incorporated with the purpose of combining two commonly held companies, Wave Life Sciences USA, Inc. ("Wave USA"), a Delaware corporation (formerly Ontorii, Inc.), and Wave Life Sciences Japan, Inc. ("Wave Japan"), a company organized under the laws of Japan (formerly Chiralgen., Ltd.), which occurred on September 13, 2012. On May 31, 2016, Wave Life Sciences Ireland Limited ("Wave Ireland") was formed as a wholly-owned subsidiary of Wave Life Sciences Ltd. On April 3, 2017, Wave Life Sciences UK Limited ("Wave UK") was formed as a wholly-owned subsidiary of Wave Life Sciences Ltd.

The Company's primary activities since inception have been developing and evolving PRISM to design, develop and commercialize oligonucleotide therapeutics, advancing the Company's differentiated neurology portfolio, as well as exploring other therapeutic areas of interest, building the Company's research and development capabilities, advancing programs into the clinic, furthering clinical development of such clinical-stage programs, building the Company's intellectual property, and assuring adequate capital to support these activities.

Liquidity

Since its inception, the Company has not generated any product revenue and has incurred recurring net losses. To date, the Company has primarily funded its operations through private placements of debt and equity securities, public offerings of its ordinary shares and collaborations with third parties. Until the Company can generate significant revenue from product sales, if ever, the Company expects to continue to finance operations through a combination of public or private equity or debt financings or other sources, which may include collaborations with third parties. Adequate additional financing may not be available to the Company on acceptable terms, or at all. The inability to raise capital as and when needed would have a negative impact on the Company's financial condition and ability to pursue its business strategy.

As of December 31, 2020, the Company had cash and cash equivalents of $184.5 million. The Company expects that its existing cash and cash equivalents will be sufficient to fund its operations for at least the next twelve months. The Company has based this expectation on assumptions that may prove to be incorrect, and the Company may use its available capital resources sooner than it currently expects. If the Company's anticipated operating results are not achieved in future periods, planned expenditures may need to be further reduced in order to extend the time period over which the then-available resources would be able to fund the Company's operations. In addition, the Company may elect to raise additional funds before it needs them if the conditions for raising capital are favorable due to market conditions or strategic considerations, even if the Company expects it has sufficient funds for its current or future operating plans.

Risks and Uncertainties

The Company is subject to risks common to companies in the biotechnology industry including, but not limited to, new technological innovations, protection of proprietary technology, maintaining internal manufacturing capabilities, dependence on key personnel, compliance with government regulations and the need to obtain additional financing. The Company's therapeutic programs will require significant additional research and development efforts, including extensive preclinical and clinical testing and regulatory approval, prior to commercialization of any product candidates. These efforts require significant amounts of additional capital, adequate personnel infrastructure and extensive compliance-reporting capabilities. There can be no assurance that the Company's research and development efforts will be successful, that adequate protection for the Company's intellectual property will be obtained, that any products developed will obtain necessary government regulatory approval or that any approved products will be commercially viable. Even if the Company's product development efforts are successful, it is uncertain when, if ever, the Company will generate significant revenue from product sales. The Company operates in an environment of rapid change in technology and substantial competition from pharmaceutical and biotechnology companies.

Basis of Presentation

The Company has prepared the accompanying consolidated financial statements in conformity with generally accepted accounting principles in the United States ("U.S. GAAP") and in U.S. dollars.

2. SIGNIFICANT ACCOUNTING POLICIES

Cash Equivalents

The Company considers all highly liquid securities with original final maturities of three months or less from the date of purchase to be cash equivalents. Cash equivalents are comprised of funds in money market accounts.

Principles of Consolidation

The Company's consolidated financial statements include the accounts of the Company and its wholly-owned subsidiaries. All intercompany balances and transactions have been eliminated in consolidation.

Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of expenses during the reporting periods. Significant estimates and assumptions reflected in these consolidated financial statements include the assumptions used to determine the fair value of share-based awards, the Company's revenue recognition policy, particularly, (a) assessing the number of performance obligations; (b) determining the transaction price; (c) allocating the transaction price to the performance obligations in the contract; and (d) determining the pattern over which performance obligations are satisfied, including estimates to complete performance obligations, the evaluation of progress to completion of external research and development costs which can result in prepaid or accrued expenses related to the Company's contract research organizations ("CROs") and contract manufacturing organizations ("CMOs"), the valuation allowance required for the Company's deferred tax assets, determining uncertain tax positions and the related liabilities, and estimating refundable tax credits. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. Actual results could differ from the Company's estimates.

Segment Data

The Company manages its operations as a single segment for the purposes of assessing performance and making operating decisions. The Company's singular focus is on developing its proprietary discovery and drug development platform, PRISM, to develop and commercialize a broad pipeline of nucleic acid-based therapeutics, or oligonucleotides.

Going Concern

At each reporting period, the Company evaluates whether there are conditions or events that raise substantial doubt about the Company's ability to continue as a going concern within one year after the date that the financial statements are issued. The Company is required to make certain additional disclosures if it concludes substantial doubt exists and it is not alleviated by the Company's plans or when its plans alleviate substantial doubt about the Company's ability to continue as a going concern. The Company's evaluation entails analyzing prospective operating budgets and forecasts for expectations of the Company's cash needs and comparing those needs to the current cash and cash equivalent balance.

Foreign Currency Translation

The functional currency is the U.S. dollar for all of the Company's entities aside from Wave Japan, which has the Japanese Yen as its functional currency. Assets and liabilities of Wave Japan are translated at period end exchange rates while revenues and expenses of Wave Japan are translated at average exchange rates for the period. Net unrealized gains and losses from foreign currency translation are reflected as other comprehensive income (loss) within the consolidated statements of Series A preferred shares and shareholders' equity and the consolidated statements of operations and comprehensive loss. Gains and losses on foreign currency transactions are included in the consolidated statements of operations and comprehensive loss within other income, net.

Fair Value of Financial Instruments

The Company is required to disclose information on all assets and liabilities reported at fair value that enables an assessment of the inputs used in determining the reported fair values. The fair value hierarchy is a hierarchy of inputs used in measuring fair value that maximizes the use of observable inputs and minimizes the use of unobservable inputs by requiring that the observable inputs be used

when available. Observable inputs are inputs that market participants would use in pricing the financial instrument based on market data obtained from sources independent of the Company. Unobservable inputs are inputs that reflect the Company's assumptions about the inputs that market participants would use in pricing the financial instrument and are developed based on the information available in the circumstances. The fair value hierarchy applies only to the valuation inputs used in determining the reported fair value of the investments and is not a measure of the investment credit quality. The hierarchy defines three levels of valuation inputs:

Level 1—Unadjusted quoted prices in active markets that are accessible at the measurement date of identical, unrestricted assets.

Level 2—Quoted prices for similar assets, or inputs that are observable, either directly or indirectly, for substantially the full term through corroboration with observable market data. Level 2 includes investments valued at quoted prices adjusted for legal or contractual restrictions specific to the security.

Level 3—Pricing inputs are unobservable for the asset, that is, inputs that reflect the reporting entity's own assumptions about the assumptions market participants would use in pricing the asset. Level 3 includes private investments that are supported by little or no market activity.

Cash, cash equivalents and restricted cash are Level 1 assets which are comprised of funds held in checking and money market accounts. Cash, cash equivalents and restricted cash were recorded at fair value as of December 31, 2020 and 2019, totaling $188.1 million and $150.8 million, respectively. The carrying amounts of accounts payable and accrued expenses approximate their fair values due to their short-term maturities. Accounts receivable relate to the Company's collaboration agreements.

Concentration of Credit Risk

Cash and cash equivalents are financial instruments that potentially subject the Company to concentration of credit risk. The Company uses several financial institutions to maintain its cash and cash equivalents, all of which are high quality, accredited financial institutions and, accordingly, such funds are subject to minimal credit risk. The Company has not experienced any losses in such accounts and management believes that the Company is not exposed to significant credit risk due to the financial position of the depository institutions in which those deposits are held. The Company has no financial instruments with off-balance sheet risk of loss.

Restricted Cash

Restricted cash consists primarily of cash placed in separate restricted bank accounts as required under the terms of the Company's lease agreements for its Cambridge, Massachusetts and Lexington, Massachusetts facilities (refer to Note 8). As of December 31, 2020 and 2019, the Company had $3.7 million and $3.6 million of restricted cash, respectively, of which $1.0 million related to the Cambridge facility and the remainder related to the Lexington facility.

Property and Equipment

Property and equipment, which consists primarily of equipment, furniture, software and leasehold improvements, are stated at cost less accumulated depreciation. Depreciation is calculated on a straight-line basis over the following estimated useful lives of the assets:

Equipment, Furniture and Software	3-7 years
Leasehold Improvements	Shorter of asset life or lease term

Depreciation begins at the time the asset is placed in service. Maintenance and repairs are charged to operations as incurred. Upon retirement or sale, the cost of the disposed asset and the related accumulated depreciation are removed from the accounts and any resulting gain or loss is reflected in the consolidated statements of operations and comprehensive loss.

Impairment of Long-Lived Assets

Long-lived assets consist of property and equipment. Long-lived assets are reviewed for impairment whenever events or other changes in circumstances indicate that the carrying amount may not be recoverable. Certain factors may exist or events may occur that indicate that impairment exists including, but not limited to, the following: significant underperformance relative to historical or projected future operating results; significant changes in the manner of use of the underlying assets; and significant adverse industry or market economic trends.

When performing the impairment assessment for long-lived assets, the Company compares the carrying value of such assets to the estimated undiscounted future net cash flows expected from the use of the assets and their eventual disposition. In the event that the carrying value of the assets is determined to be unrecoverable, the Company would estimate the fair value of the assets and record an impairment charge for the excess of the carrying value over the fair value.

Revenue Recognition

The Company recognizes revenue in accordance with Accounting Standards Codification ("ASC") Topic 606, Revenue from Contracts with Customers ("ASC 606").

This standard applies to all contracts with customers, except for contracts that are within the scope of other standards, such as leases, insurance, and financial instruments. Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration that the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of ASC 606, the entity performs the following five-step analysis: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the entity satisfies a performance obligation. The Company only applies the five-step analysis to contracts when it is probable that the entity will collect the consideration to which it is entitled in exchange for the goods or services it transfers to the customer. At contract inception, once the contract is determined to be within the scope of ASC 606, the Company assesses the goods or services promised within each contract, determines those that are performance obligations, and assesses whether each promised good or service is distinct. The Company then recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) the performance obligation is satisfied.

The Company has entered into collaboration agreements for research, development, and commercial services, under which the Company licenses certain rights to its product candidates to third parties. The terms of these arrangements typically include payment to the Company of one or more of the following: non-refundable, upfront license fees; reimbursement of certain costs; customer option exercise fees; development, regulatory and commercial milestone payments; and royalties on net sales of licensed products. Any variable consideration is constrained and, therefore, the cumulative revenue associated with this consideration is not recognized until it is deemed not to be at significant risk of reversal.

In determining the appropriate amount of revenue to be recognized as the Company fulfills its obligations under each of its agreements for which the collaboration partner is also a customer, the Company performs the following steps: (i) identification of the promised goods or services in the contract; (ii) determination of whether the promised goods or services are performance obligations, including whether they are distinct in the context of the contract; (iii) measurement of the transaction price, including the constraint on variable consideration; (iv) allocation of the transaction price to the performance obligations; and (v) recognition of revenue when (or as) the Company satisfies each performance obligation. As part of the accounting for these arrangements, the Company must use significant judgment to determine: (a) the number of performance obligations based on the determination under step (ii) above; (b) the transaction price under step (iii) above; and (c) the timing of satisfaction of performance obligations as a measure of progress in step (v) above. The Company uses significant judgment to determine whether milestones or other variable consideration, except for royalties, should be included in the transaction price as described further below. The transaction price is allocated to the optional goods and services the Company expects to provide. The Company uses estimates to determine the timing of satisfaction of performance obligations.

Amounts received prior to being recognized as revenue are recorded as deferred revenue. Amounts expected to be recognized as revenue within the 12 months following the balance sheet date are classified as current portion of deferred revenue in the accompanying consolidated balance sheets. Amounts not expected to be recognized as revenue within the 12 months following the balance sheet date are classified as deferred revenue, net of current portion.

Licenses of intellectual property: In assessing whether a promise or performance obligation is distinct from the other promises, the Company considers factors such as the research, development, manufacturing and commercialization capabilities of the customer and the availability of the associated expertise in the general marketplace. In addition, the Company considers whether the customer can benefit from a promise for its intended purpose without the receipt of the remaining promise, whether the value of the promise is dependent on the unsatisfied promise, whether there are other vendors that could provide the remaining promise, and whether it is separately identifiable from the remaining promise. For licenses that are combined with other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Research and development services: If an arrangement is determined to contain a promise or obligation for the Company to perform research and development services, the Company must determine whether these services are distinct from other promises in the arrangement. In assessing whether the services are distinct from the other promises, the Company considers the capabilities of the customer to perform these same services. In addition, the Company considers whether the customer can benefit from a promise for its intended purpose without the receipt of the remaining promise, whether the value of the promise is dependent on the unsatisfied promise, whether there are other vendors that could provide the remaining promise, and whether it is separately identifiable from the remaining promise. For research and development services that are combined with other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time

and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

Customer options: If an arrangement is determined to contain customer options that allow the customer to acquire additional goods or services, the goods and services underlying the customer options are not considered to be performance obligations at the outset of the arrangement, as they are contingent upon option exercise. The Company evaluates the customer options for material rights, that is, the option to acquire additional goods or services for free or at a discount. If the customer options are determined to represent a material right, the material right is recognized as a separate performance obligation at the outset of the arrangement. The Company allocates the transaction price to material rights based on the standalone selling price. As a practical alternative to estimating the standalone selling price when the goods or services are both (i) similar to the original goods and services in the contract and (ii) provided in accordance with the terms of the original contract, the Company allocates the total amount of consideration expected to be received from the customer to the total goods or services expected to be provided to the customer. Amounts allocated to any material right are not recognized as revenue until the option is exercised and the performance obligation is satisfied.

Milestone payments: At the inception of each arrangement that includes milestone payments, the Company evaluates whether a significant reversal of cumulative revenue provided in conjunction with achieving the milestones is probable, and estimates the amount to be included in the transaction price using the most likely amount method. If it is probable that a significant reversal of cumulative revenue would not occur, the associated milestone value is included in the transaction price. Milestone payments that are not within the control of the Company or the licensee, such as regulatory approvals, are not considered probable of being achieved until those approvals are received. For other milestones, the Company evaluates factors such as the scientific, clinical, regulatory, commercial, and other risks that must be overcome to achieve the particular milestone in making this assessment. There is considerable judgment involved in determining whether it is probable that a significant reversal of cumulative revenue would not occur. At the end of each subsequent reporting period, the Company reevaluates the probability of achievement of all milestones subject to constraint and, if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues and earnings in the period of adjustment.

Royalties: For arrangements that include sales-based royalties, including milestone payments based on a level of sales, and the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied (or partially satisfied). To date, the Company has not recognized any royalty revenue resulting from any of its licensing arrangements.

Contract costs: The Company recognizes as an asset the incremental costs of obtaining a contract with a customer if the costs are expected to be recovered. As a practical expedient, the Company recognizes the incremental costs of obtaining a contract as an expense when incurred if the amortization period of the asset that it otherwise would have recognized is one year or less. To date, the Company has not incurred any incremental costs of obtaining a contract with a customer.

For additional discussion of accounting for collaboration revenues, see Note 5.

Research and Development Expenses

Research and development expenses are expensed as incurred. External development costs are recognized based on an evaluation of the progress to completion of specific tasks. Payments for these activities are based on the terms of the individual agreements, which may differ from the pattern of costs incurred, and are reflected in the accompanying consolidated balance sheets as prepaid or accrued expenses.

License Agreements and Patent Costs

Costs associated with licenses of technology and patent costs are expensed as incurred and are generally included in research and development expense in the consolidated statements of operations and comprehensive loss.

Refundable Tax Credits

The Company is eligible for refundable tax credits with tax authorities for certain qualified operating expenses. The Company recognizes refundable tax credits when there is reasonable assurance that the Company will comply with the requirements of the refundable tax credit and that the refundable tax credit will be received.

Refundable tax credits are recorded as income and classified in other income, net in the consolidated statements of operations and comprehensive loss.

Net Loss per Share

Basic net loss per share is computed using the weighted-average number of ordinary shares outstanding during the period. Diluted net loss per share is computed using the sum of the weighted-average number of ordinary shares outstanding during the period and, if dilutive, the weighted-average number of potential ordinary shares, including the assumed exercise of share options.

The Company applies the two-class method to calculate its basic and diluted net loss per share attributable to ordinary shareholders, as its Series A preferred shares are participating securities. The two-class method is an earnings allocation formula that treats a participating security as having rights to earnings that otherwise would have been available to ordinary shareholders. However, for the periods presented, the two-class method does not impact the net loss per ordinary share as the Company was in a net loss position for each of the periods presented and holders of Series A preferred shares do not participate in losses.

The Company's Series A preferred shares contractually entitle the holders of such shares to participate in dividends but do not contractually require the holders of such shares to participate in losses of the Company. Accordingly, for periods in which the Company reports a net loss attributable to ordinary shareholders, diluted net loss per share attributable to ordinary shareholders is the same as basic net loss per share attributable to ordinary shareholders, since dilutive ordinary shares are not assumed to have been issued if their effect is anti-dilutive.

Share-Based Compensation

The Company measures and recognizes share-based compensation expense, for both employee and director option awards, based on the grant date fair value of the awards. The Company calculates the fair value of restricted share unit awards based on the grant date fair value of the underlying ordinary shares. The Company recognizes share-based compensation expense on a straight-line basis over the requisite service period of the awards, which is generally the vesting period.

The Company determines the fair value of share-based awards granted to non-employees as either the fair value of the consideration received or the fair value of the equity instruments issued, whichever is more reliably measurable. All equity instruments issued to non-employees as consideration for goods or services received by the Company are accounted for based on the fair value of the equity instruments issued. These awards are recorded in expense and additional paid-in capital in shareholders' equity over the applicable service periods based on the fair value of the options at the end of each period. The Company accounts for the expense from share-based awards to non-employees by re-measuring the awards at fair value over the vesting period.

The Company classifies share-based compensation expense in its consolidated statements of operations and comprehensive loss in the same manner in which the award recipient's compensation costs are classified or in which the award recipient's service payments are classified.

The fair value of each share option grant was determined using the methods and assumptions discussed below. These inputs are generally subjective and require significant judgment and estimation by management.

- *Fair Value of Ordinary Shares* The fair value of the ordinary shares underlying the Company's share-based awards is based on the closing price of the Company's ordinary shares as reported by the Nasdaq Global Market on the date of grant.
- *Expected Term* The expected term of share options represents the weighted-average period that the share options are expected to remain outstanding. The Company estimated the expected term using the simplified method, which is an average of the contractual term of the option and the vesting period.
- *Expected Volatility* Since there is limited historical data for the Company's ordinary shares and limited company-specific historical volatility, it has determined the share price volatility for options granted based on an analysis of the volatility used by a peer group of publicly traded companies. In evaluating similarity, the Company considers factors such as industry, stage of life cycle and size.
- *Risk-free Interest Rate* The risk-free interest rate is based on the U.S. Treasury yield in effect at the time of the grant for zero-coupon U.S. Treasury notes with remaining terms similar to the expected term of the options.
- *Dividend Rate* The expected dividend was assumed to be zero as the Company has never paid dividends and has no current plans to do so.

Income Taxes

The Company accounts for income taxes using an asset and liability approach, which requires recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the consolidated financial statements but have not been reflected in taxable income. A valuation allowance is established to reduce deferred tax assets to their estimated realizable value. Therefore, the Company provides a valuation allowance to the extent that it is more likely than not that all or a portion of the deferred tax assets will not be realized in the future.

The Company accounts for uncertainty in income taxes recognized in the financial statements by applying a two-step process to determine the amount of tax benefit to be recognized. First, the tax position must be evaluated to determine the likelihood that it will be sustained upon external examination by the tax authorities. If the tax position is deemed more-likely-than-not to be sustained, the tax position is then assessed to determine the amount of benefit to recognize in the financial statements. The amount of the benefit that may be recognized is the largest amount that has a greater than 50% likelihood of being realized upon ultimate settlement. The provision for income taxes includes the effects of any resulting tax reserves, or unrecognized tax benefits, that are considered appropriate as well as the related net interest and penalties.

The Company recognizes interest and penalties related to uncertain tax positions in the income tax provision on the consolidated statements of operations and comprehensive loss.

The Company has certain service arrangements in place between its U.S., Japan, U.K. and Singapore entities, which include transfer pricing assumptions. The determination of the appropriate level of transfer pricing requires judgment based on transfer pricing analyses of comparable companies. The Company monitors the nature of its service arrangements for changes in its operations as well as economic conditions. The Company also periodically reviews the transfer pricing analyses for changes in the composition in the pool of comparable companies as well as the related ongoing results of the comparable companies.

Leases

Effective January 1, 2019, the Company adopted ASC 842, Leases (“ASC 842”), using the modified retrospective approach and utilizing the effective date as its date of initial application, for which prior periods are presented in accordance with the previous guidance in ASC 840, Leases (“ASC 840”). In February 2016, the FASB issued ASU No. 2016-02, Leases (“ASU 2016-02”), which was further clarified when the FASB issued ASU No. 2018-10, Codification Improvements to Topic 842, Leases (“ASU 2018-10”), ASU No. 2018-11, Leases (Topic 842)—Targeted Improvements (“ASU 2018-11”), and ASU No. 2019-01, Codification Improvements to Topic 842, Leases (“ASU 2019-01”). The adoption of ASC 842, in accordance with ASU 2016-02, ASU 2018-10, ASU 2018-11, and ASU 2019-01, requires a lessee to recognize assets and liabilities on the balance sheet for operating leases and changes many key definitions, including the definition of a lease. ASC 842 includes a short-term lease exception for leases with a term of 12 months or less, in which a lessee can make an accounting policy election not to recognize lease assets and lease liabilities. Lessees will continue to differentiate between finance leases (previously referred to as capital leases) and operating leases, using classification criteria that are substantially similar to the previous guidance. For lessees, the recognition, measurement, and presentation of expenses and cash flows arising from a lease have not significantly changed from previous U.S. GAAP. Lessees and lessors are required to recognize and measure leases at the beginning of the earliest period presented using a modified retrospective approach. The modified retrospective approach includes a number of optional practical expedients that entities may elect to apply, as well as transition guidance specific to nonstandard leasing transactions. As further described above, the Company adopted ASC 842 on January 1, 2019 using a cumulative-effect adjustment on the effective date of the standard, for which comparative periods are presented in accordance with the previous guidance in ASC 840.

In adopting ASC 842, the Company elected to utilize the available package of practical expedients permitted under the transition guidance within the new standard, which does not require the reassessment of the following: i) whether existing or expired arrangements are or contain a lease, ii) the lease classification of existing or expired leases, and iii) whether previous initial direct costs would qualify for capitalization under the new lease standard. Additionally, the Company made an accounting policy election to not recognize on the balance sheet leases with a term of 12 months or less.

At the inception of an arrangement, the Company determines whether the arrangement is or contains a lease based on the unique facts and circumstances present in the arrangement. Most leases with a term greater than one year are recognized on the balance sheet as right-of-use assets and short-term and long-term lease liabilities, as applicable. The Company typically only includes an initial lease term in its assessment of a lease arrangement. Options to renew a lease are not included in the Company’s assessment unless there is reasonable certainty that the Company will renew the lease. The Company monitors its plans to renew its leases on a quarterly basis.

Operating lease liabilities and their corresponding right-of-use assets are recorded based on the present value of lease payments over the expected remaining lease term. Certain adjustments to the right-of-use asset may be required for items such as incentives received. The interest rate implicit in lease contracts is typically not readily determinable. As a result, the Company utilizes its incremental borrowing rate, which reflects the fixed rate at which the Company could borrow on a collateralized basis the amount of the lease payments in the same currency, for a similar term, in a similar economic environment. In transition to ASC 842, the Company utilized the remaining lease term of its leases in determining the appropriate incremental borrowing rates.

In accordance with ASC 842, components of a lease should be split into three categories: lease components (e.g., land, building, etc.), non-lease components (e.g., common area maintenance, consumables, etc.), and non-components (e.g., property taxes, insurance, etc.). The fixed and in-substance fixed contract consideration (including any consideration related to non-components) must be allocated based on the respective relative fair values to the lease components and non-lease components.

Although separation of lease and non-lease components is required, certain expedients are available. Entities may elect the practical expedient to not separate lease and non-lease components by class of underlying asset. Rather, entities would account for each lease component and the related non-lease component together as a single component. For new and amended leases beginning in 2019 and after, the Company has elected to account for the lease and non-lease components for leases for classes of all underlying assets and allocate all of the contract consideration to the lease component only.

Recently Issued Accounting Pronouncements

In December 2019, the FASB finalized Accounting Standards Update No. 2019-12, Income Taxes (Topic 740): *Simplifying the Accounting for Income Taxes* ("ASU 2019-12"). ASU 2019-12 eliminates certain exceptions in ASC 740 and generally simplifies existing guidance. The new guidance is effective for fiscal years beginning after December 15, 2020, including interim periods within those fiscal years, but may be adopted earlier by entities. The Company is currently evaluating the potential impact that the adoption of ASU 2019-12 may have on its consolidated financial statements.

3. PROPERTY AND EQUIPMENT, NET

Property and equipment, net, consists of the following:

	December 31,	
	2020	2019
	(in thousands)	
Furniture and equipment	$ 25,418	$ 24,531
Software	684	524
Leasehold improvements	27,912	27,830
Fixed assets in progress	78	486
Total	54,092	53,371
Less accumulated depreciation	(24,894)	(17,003)
Property and equipment, net	$ 29,198	$ 36,368

Substantially all of the Company's long-lived assets were located in the United States as of December 31, 2020 and 2019.

Depreciation expense was $8.1 million and $7.6 million for the years ended December 31, 2020 and 2019, respectively.

4. ACCRUED EXPENSES AND OTHER CURRENT LIABILITIES

Accrued expenses and other current liabilities consist of the following:

	December 31,	
	2020	2019
	(in thousands)	
Accrued compensation	$ 9,003	$ 8,662
Accrued expenses related to CROs and CMOs	2,143	5,030
Accrued expenses and other current liabilities	825	2,493
Total accrued expenses and other current liabilities	$ 11,971	$ 16,185

5. COLLABORATION AGREEMENTS

Pfizer Collaboration and Equity Agreements

In May 2016, the Company entered into a Research, License and Option Agreement (as amended in November 2017, the "Pfizer Collaboration Agreement") with Pfizer Inc. ("Pfizer"). Pursuant to the terms of the Pfizer Collaboration Agreement, the Company and Pfizer agreed to collaborate on the discovery, development and commercialization of stereopure oligonucleotide therapeutics for up to five programs (the "Pfizer Programs"), each directed at a genetically-defined hepatic target selected by Pfizer (the "Pfizer Collaboration"). The Company received $10.0 million as an upfront license fee under the Pfizer Collaboration Agreement. Subject to option exercises by Pfizer, the Company was entitled to earn potential research, development and commercial milestone payments, plus royalties, tiered up to low double-digits, on sales of any products that may result from the Pfizer Collaboration. None of the payments under the Pfizer Collaboration Agreement are refundable.

Simultaneously with the entry into the Pfizer Collaboration Agreement, the Company entered into a Share Purchase Agreement (the "Pfizer Equity Agreement," and together with the Pfizer Collaboration Agreement, the "Pfizer Agreements") with C.P. Pharmaceuticals International C.V., an affiliate of Pfizer (the "Pfizer Affiliate"). Pursuant to the terms of the Pfizer Equity Agreement, the Pfizer Affiliate purchased 1,875,000 of the Company's ordinary shares (the "Shares") at a purchase price of $16.00 per share, for an aggregate purchase price of $30.0 million. The Company did not incur any material costs in connection with the issuance of the Shares.

Under the Pfizer Collaboration Agreement, the parties agreed to collaborate during a four-year research term. During the research term, the Company was responsible to use its commercially reasonable efforts to advance up to five programs through to the selection of clinical candidates. At that stage, Pfizer was entitled to elect to license any of these Pfizer Programs exclusively and obtain exclusive rights to undertake the clinical development of the resulting clinical candidates into products and the potential commercialization of any such products thereafter. In addition, the Company received a non-exclusive, royalty-bearing sublicensable license to use Pfizer's hepatic targeting technology in any of the Company's own hepatic programs that are outside the scope of the Pfizer Collaboration (the "Wave Programs"). If the Company uses this technology on the Wave Programs, Pfizer is eligible to receive potential development and commercial milestone payments from the Company. Pfizer is also eligible to receive tiered royalties on sales of any products that include Pfizer's hepatic targeting technology. The Company is not currently utilizing Pfizer's hepatic targeting technology in any of its own hepatic programs that are outside of the scope of the Pfizer Collaboration Agreement.

The stated term of the Pfizer Collaboration Agreement commenced on May 5, 2016 and terminates on the date of the last to expire payment obligation with respect to each Pfizer Program and, with respect to each Wave Program, expires on a program-by-program basis accordingly. Pfizer may terminate its rights related to a Pfizer Program under the Pfizer Collaboration Agreement at its own convenience upon 90 days' notice to the Company. The Company may also terminate its rights related to a Wave Program at its own convenience upon 90 days' notice to Pfizer. The Pfizer Collaboration Agreement may also be terminated by either party in the event of an uncured material breach of the Pfizer Collaboration Agreement by the other party.

Pfizer nominated two hepatic targets upon entry into the Pfizer Collaboration in May 2016. The Pfizer Collaboration Agreement provided Pfizer with options to nominate up to three additional programs by making nomination milestone payments. Pfizer nominated the third, fourth and fifth hepatic targets in August 2016, March 2018 and April 2018, respectively.

The Pfizer Collaboration is managed by a joint steering committee in which both parties are represented equally, which will oversee the scientific progression of each Pfizer Program up to the clinical candidate stage. During the four-year research term and for a period of two years thereafter, the Company has agreed to work exclusively with Pfizer with respect to using any of the Company's stereopure oligonucleotide technology that is specific for the applicable hepatic target which is the basis of any Pfizer Program. Within a specified period after receiving a data package for a candidate under each nominated program, Pfizer may exercise an option to obtain a license to develop, manufacture and commercialize the program candidate by paying an exercise price per program.

The Company assessed this arrangement in accordance with ASC 606 and concluded that the contract counterparty, Pfizer, is a customer. The Company identified the following promises under the arrangement: (1) the non-exclusive, royalty-free research and development license; (2) the research and development services for Programs 1 and 2; (3) the program nomination options for Programs 3, 4 and 5; (4) the research and development services associated with Programs 3, 4 and 5; (5) the options to obtain a license to develop, manufacture and commercialize Programs 1 and 2; and (6) the options to obtain a license to develop, manufacture and commercialize Programs 3, 4 and 5. The research and development services for each of Programs 1 and 2 were determined to not be distinct from the research and development license and should be combined into a single performance obligation for each program. The promises under the Pfizer Collaboration Agreement relate primarily to the research and development required by the Company for each of the programs nominated by Pfizer.

Additionally, the Company determined that the program nomination options for Programs 3, 4 and 5 were priced at a discount and, as such, provide material rights to Pfizer, representing three separate performance obligations. The research and development services associated with Programs 3, 4 and 5 and the options to obtain a license to develop, manufacture and commercialize Programs 3, 4 and 5 are subject to Pfizer's exercise of the program nomination options for such programs and therefore do not represent performance obligations at the outset of the arrangement. The options to obtain a license to develop, manufacture and commercialize Programs 1

and 2 do not represent material rights; as such, they are not representative of performance obligations at the outset of the arrangement. Based on these assessments, the Company identified five performance obligations in the Pfizer Collaboration Agreement: (1) research and development services and license for Program 1; (2) research and development services and license for Program 2; (3) material right provided for the option to nominate Program 3; (4) material right provided for the option to nominate Program 4; and (5) material right provided for the option to nominate Program 5.

At the outset of the arrangement, the transaction price included only the $10.0 million up-front consideration received. The Company determined that the Pfizer Collaboration Agreement did not contain a significant financing component. The program nomination option exercise fees for research and development services associated with Programs 3, 4 and 5 that may be received are excluded from the transaction price until each customer option is exercised. The potential milestone payments were excluded from the transaction price, as all milestone amounts were fully constrained at the inception of the Pfizer Collaboration Agreement. The exercise fees for the options to obtain a license to develop, manufacture and commercialize Programs 3, 4 and 5 that may be received are excluded from the transaction price until each customer option is exercised. The Company will reevaluate the transaction price at the end of each reporting period and as uncertain events are resolved or other changes in circumstances occur, and, if necessary, will adjust its estimate of the transaction price.

During the year ended December 31, 2017, it became probable that a significant reversal of cumulative revenue would not occur for a developmental milestone under the Pfizer Collaboration Agreement. At such time, the associated consideration was added to the estimated transaction price and allocated to the existing performance obligations, and the Company recognized a cumulative catch-up to revenue for this developmental milestone, representing the amount that would have been recognized had the milestone payment been included in the transaction price from the outset of the arrangement. The remainder will be recognized in the same manner as the remaining, unrecognized transaction price over the remaining period until each performance obligation is satisfied.

Revenue associated with the performance obligations relating to Programs 1 and 2 is being recognized as revenue as the research and development services are provided using an input method, according to the full-time employee (“FTE”) hours incurred on each program and the FTE hours expected to be incurred in the future to satisfy the performance obligation. The transfer of control occurs over time and, in management’s judgment, this input method is the best measure of progress towards satisfying the performance obligation. The amount allocated to the three material rights will be recognized as the underlying research and development services are provided commencing from the date that Pfizer exercises each respective option, or immediately as each option expires unexercised. The amounts received that have not yet been recognized as revenue are recorded in deferred revenue on the Company’s consolidated balance sheet.

Pfizer nominated the third, fourth and fifth hepatic targets in August 2016, March 2018 and April 2018, respectively. Upon each exercise, the Company allocated the transaction price amount allocated to the material right at inception of the arrangement plus the program nomination option exercise fee paid by Pfizer at the time of exercising the option to a new performance obligation, which will be recognized as revenue as the research and development services are provided using the same method as the performance obligations relating to Programs 1 and 2.

The research term for the Pfizer Collaboration Agreement ended by its original terms in May 2020. Through December 31, 2020, the Company had recognized revenue of $18.5 million as collaboration revenue in the Company’s consolidated statements of operations and comprehensive loss under the Pfizer Collaboration Agreement. During the years ended December 31, 2020 and 2019, the Company recognized revenue of $1.5 million and $7.1 million, respectively, under the Pfizer Collaboration Agreement.

Takeda Collaboration and Equity Agreements

In February 2018, Wave USA and Wave UK entered into a global strategic collaboration (the "Takeda Collaboration") with Takeda Pharmaceutical Company Limited ("Takeda"), pursuant to which Wave USA, Wave UK and Takeda agreed to collaborate on the research, development and commercialization of oligonucleotide therapeutics for disorders of the Central Nervous System ("CNS"). The Takeda Collaboration provides Wave with at least $230.0 million in committed cash and Takeda with the option to co-develop and co-commercialize Wave's CNS development programs in (1) Huntington's disease ("HD"); (2) amyotrophic lateral sclerosis ("ALS") and frontotemporal dementia ("FTD"); and (3) Wave's discovery-stage program targeting *ATXN3* for the treatment of spinocerebellar ataxia 3 ("SCA3") (collectively, "Category 1 Programs"). In addition, Takeda will have the right to exclusively license multiple preclinical programs for CNS disorders, including Alzheimer's disease and Parkinson's disease (collectively, "Category 2 Programs"). In April 2018, the Takeda Collaboration became effective and Takeda paid Wave $110.0 million as an upfront payment. Takeda also agreed to fund Wave's research and preclinical activities in the amount of $60.0 million during the four-year research term and to reimburse Wave for any collaboration-budgeted research and preclinical expenses incurred by Wave that exceed that amount.

Simultaneously with Wave USA and Wave UK's entry into the collaboration and license agreement with Takeda (the "Takeda Collaboration Agreement"), the Company entered into a share purchase agreement with Takeda (the "Takeda Equity Agreement," and together with the Takeda Collaboration Agreement, the "Takeda Agreements") pursuant to which it agreed to sell to Takeda 1,096,892 of its ordinary shares at a purchase price of $54.70 per share. In April 2018, the Company closed the Takeda Equity Agreement and received aggregate cash proceeds of $60.0 million. The Company did not incur any material costs in connection with the issuance of shares.

With respect to Category 1 Programs, Wave will be responsible for researching and developing products and companion diagnostics for Category 1 Programs through completion of the first proof of mechanism study for such products. Takeda will have an exclusive option for each target and all associated products and companion diagnostics for such target, which it may exercise at any time through completion of the proof of mechanism study. If Takeda exercises this option, Wave will receive an opt-in payment and will lead manufacturing and joint clinical co-development activities and Takeda will lead joint co-commercial activities in the United States and all commercial activities outside of the United States. Global costs and potential profits will be shared 50:50 and Wave will be eligible to receive development and commercial milestone payments. In addition to its 50% profit share, Wave is eligible to receive option exercise fees and development and commercial milestone payments for each of the Category 1 Programs.

With respect to Category 2 Programs, Wave has granted Takeda the right to exclusively license multiple preclinical programs during a four-year research term (subject to limited extension for programs that were initiated prior to the expiration of the research term, in accordance with the Takeda Collaboration Agreement) ("Category 2 Research Term"). During that term, the parties may collaborate on preclinical programs for up to six targets at any one time. Wave will be responsible for researching and preclinically developing products and companion diagnostics directed to the agreed upon targets through completion of Investigational New Drug application ("IND")-enabling studies in the first major market country. Thereafter, Takeda will have an exclusive worldwide license to develop and commercialize products and companion diagnostics directed to such targets, subject to Wave's retained rights to lead manufacturing activities for products directed to such targets. Takeda will fund Wave's research and preclinical activities in the amount of $60.0 million during the research term and will reimburse Wave for any collaboration-budgeted research and preclinical expenses incurred by Wave that exceed that amount. Wave is also eligible to receive tiered high single-digit to mid-teen royalties on Takeda's global commercial sales of products from each Category 2 Program.

Under the Takeda Collaboration Agreement, each party grants to the other party specific intellectual property licenses to enable the other party to perform its obligations and exercise its rights under the Takeda Collaboration Agreement, including license grants to enable each party to conduct research, development and commercialization activities pursuant to the terms of the Takeda Collaboration Agreement.

The term of the Takeda Collaboration Agreement commenced on April 2, 2018 and, unless terminated earlier, will continue until the date on which: (i) with respect to each Category 1 Program target for which Takeda does not exercise its option, the expiration or termination of the development program with respect to such target; (ii) with respect to each Category 1 Program target for which Takeda exercises its option, the date on which neither party is researching, developing or manufacturing any products or companion diagnostics directed to such target; or (iii) with respect to each Category 2 Program target, the date on which royalties are no longer payable with respect to products directed to such target.

Takeda may terminate the Takeda Collaboration Agreement for convenience on 180 days' notice, in its entirety or on a target-by-target basis. Subject to certain exceptions, each party has the right to terminate the Takeda Collaboration Agreement on a target-by-target basis if the other party, or a third party related to such party, challenges the patentability, enforceability or validity of any patents within the licensed technology that cover any product or companion diagnostic that is subject to the Takeda Collaboration Agreement. In the event of any material breach of the Takeda Collaboration Agreement by a party, subject to cure rights, the other party may terminate the Takeda Collaboration Agreement in its entirety if the breach relates to all targets or on a target-by-target basis if the breach relates to a specific target. In the event that Takeda and its affiliates cease development, manufacturing and commercialization activities with respect to compounds or products subject to the Takeda Collaboration Agreement and directed to a particular target, Wave may terminate the Takeda Collaboration Agreement with respect to such target. Either party may terminate the Takeda Collaboration Agreement for the other party's insolvency. In certain termination circumstances, Wave would receive a license from Takeda to continue researching, developing and manufacturing certain products, and companion diagnostics.

The Takeda Collaboration is managed by a joint steering committee in which both parties are represented equally. The joint steering committee is tasked with overseeing the scientific progression of each Category 1 Program and the Category 2 Programs.

The Company assessed this arrangement in accordance with ASC 606 and concluded that the contract counterparty, Takeda, is a customer for Category 1 Programs prior to Takeda exercising its option, and for Category 2 Programs during the Category 2 Research Term. The Company identified the following material promises under the arrangement: (1) the non-exclusive, royalty-free research and development license for each Category 1 Program; (2) the research and development services for each Category 1 Program through completion of the first proof of mechanism study; (3) the exclusive option to license, co-develop and co-commercialize each Category 1 Program; (4) the right to exclusively license the Category 2 Programs; and (5) the research and preclinical development services of the Category 2 Programs through completion of IND-enabling studies. The research and development services for each Category 1 Program were determined to not be distinct from the research and development license and should therefore be combined into a single performance obligation for each Category 1 Program. The research and preclinical development services for the Category 2 Programs were determined to not be distinct from the exclusive licenses for the Category 2 Programs and should therefore be combined into a single performance obligation.

Additionally, the Company determined that the exclusive option for each Category 1 Program was priced at a discount and, as such, provide material rights to Takeda, representing three separate performance obligations. Based on these assessments, the Company identified seven performance obligations in the Takeda Collaboration Agreement: (1) research and development services through completion of the first proof of mechanism and non-exclusive research and development license for HD; (2) research and development services through completion of the first proof of mechanism and non-exclusive research and development license for ALS and FTD; (3) research and development services through completion of the first proof of mechanism and non-exclusive research and development license for SCA3; (4) the material right provided for the exclusive option to license, co-develop and co-commercialize HD; (5) the material right provided for the exclusive option to license, co-develop and co-commercialize ALS and FTD; (6) the material right provided for the exclusive option to license, co-develop and co-commercialize SCA3; and (7) the research and preclinical development services and right to exclusively license the Category 2 Programs.

At the outset of the arrangement, the transaction price included the $110.0 million upfront consideration received and the $60.0 million of committed research and preclinical funding for the Category 2 Programs. The Company determined that the Takeda Collaboration Agreement did not contain a significant financing component. The option exercise fees to license, co-develop and co-commercialize each Category 1 Program that may be received are excluded from the transaction price until each customer option is exercised. The potential milestone payments were excluded from the transaction price, as all milestone amounts were fully constrained at the inception of the Takeda Collaboration Agreement. The Company will reevaluate the transaction price at the end of each reporting period and, as uncertain events are resolved or other changes in circumstances occur, if necessary, will adjust its estimate of the transaction price.

The Company allocated the transaction price to the performance obligations on a relative standalone selling price basis. For the performance obligations associated with the research and development services through completion of the first proof of mechanism and non-exclusive research and development license for HD; the research and development services through completion of the first proof of mechanism and non-exclusive research and development license for ALS and FTD; the research and development services through completion of the first proof of mechanism and non-exclusive research and development license for SCA3; and the research and preclinical development services and right to exclusively license the Category 2 Programs, the Company determined the standalone selling price using estimates of the costs to perform the research and development services, including expected internal and external costs for services and supplies, adjusted to reflect a profit margin. The total estimated cost of the research and development services reflected the nature of the services to be performed and the Company's best estimate of the length of time required to perform the services. For the performance obligations associated with the material right provided for the exclusive option to license, co-develop and co-commercialize HD; the material right provided for the exclusive option to license, co-develop and co-commercialize ALS and FTD; and the material right provided for the exclusive option to license, co-develop and co-commercialize SCA3, the Company estimated the standalone fair value of the option to license each Category 1 Program utilizing an adjusted market assessment approach, and determined that any standalone fair value in excess of the amounts to be paid by Takeda associated with each option represented a material right.

Revenue associated with the research and development services for each Category 1 Program performance obligation is being recognized as the research and development services are provided using an input method, according to the costs incurred on each Category 1 Program and the total costs expected to be incurred to satisfy each Category 1 Program performance obligation. Revenue associated with the research and preclinical development services for the Category 2 Programs performance obligation is being recognized as the research and preclinical development services are provided using an input method, according to the costs incurred on Category 2 Programs and the total costs expected to be incurred to satisfy the performance obligation. The transfer of control for these performance obligations occurs over time and, in management's judgment, this input method is the best measure of progress towards satisfying the performance obligations. The amount allocated to the material right for each Category 1 Program option will be recognized on the date that Takeda exercises each respective option, or immediately as each option expires unexercised. The amounts received that have not yet been recognized as revenue are recorded in deferred revenue on the Company's consolidated balance sheet.

Through December 31, 2020, the Company had recognized revenue of $37.0 million under the Takeda Collaboration Agreement as collaboration revenue in the Company's consolidated statements of operations and comprehensive loss. During the years ended December 31, 2020 and 2019, the Company recognized revenue of $18.6 million and $8.8 million, respectively, under the Takeda Collaboration Agreement in the Company's consolidated statements of operations and comprehensive loss. The aggregate amount of the transaction price allocated to the Company's unsatisfied and partially unsatisfied performance obligations and recorded in deferred revenue at December 31, 2020 is $133.0 million, of which $91.6 million is included in current liabilities. The Company expects to recognize revenue for the portion of the deferred revenue that relates to the research and development services for each Category 1 Program and the Category 2 Programs as costs are incurred over the remaining research term. The Company expects to recognize revenue for the portion of the deferred revenue that relates to the material right for each Category 1 Program option upon Takeda's exercise of such option, or immediately as each option expires unexercised. The aggregate amount of the transaction price included in accounts receivable at December 31, 2020 is $30.0 million, all of which is included in current assets.

6. SHARE CAPITAL

The following represents the historical ordinary share transactions of the Company from December 31, 2018 through December 31, 2020:

- In January 2019, the Company closed a follow-on underwritten public offering of 3,950,000 ordinary shares at a purchase price of $38.00 per share for gross proceeds of $150.1 million, and in February 2019 the Company closed the sale of an additional 592,500 ordinary shares (collectively, the “January 2019 Offering”) for gross proceeds of an additional $22.5 million. The net proceeds to the Company from the January 2019 Offering were $161.8 million, after deducting underwriting discounts and commissions and offering expenses.
- In September 2020, the Company closed a follow-on underwritten public offering of 8,333,334 ordinary shares at a purchase price of $12.00 per share for gross proceeds of $100.0 million (the “September 2020 Offering”). The net proceeds to the Company from the September 2020 Offering were $93.7 million, after deducting underwriting discounts and commissions and offering expenses.
- The Company entered into an open market sales agreement with Jefferies LLC in May 2019, as amended in March 2020, for its at-the-market equity program. The Company first sold shares under the at-the-market equity program in 2020. During the year ended December 31, 2020, the Company sold 5,583,022 ordinary shares under its at-the-market equity program for aggregate net proceeds of $59.9 million, after deducting commissions and offering expenses.

Features of the Series A Preferred Shares and Ordinary Shares

The Series A preferred shares and ordinary shares have no par value and there is no concept of authorized share capital under Singapore law. The Series A preferred shares are not redeemable.

Voting

The holders of Series A preferred shares are not entitled to vote on any of the matters proposed to shareholders, other than as specified in the Company's Constitution. The holders of ordinary shares are entitled to one vote for each ordinary share held at all meetings of shareholders and written actions in lieu of meetings.

Dividends

All dividends, if any, shall be declared and paid pro rata according to the number of shares held by each member entitled to receive dividends. The Company’s board of directors may deduct from any dividend all sums of money presently payable by the member to the Company on account of calls.

Liquidation

In the event of a liquidation, dissolution or winding up of, or a return of capital by the Company, the ordinary shares will rank equally with the Series A preferred shares after the payment of the liquidation preference of an aggregate of approximately $10 thousand for Series A preferred shares.

7. SHARE-BASED COMPENSATION

In December 2014, the Company's board of directors adopted the Wave Life Sciences Ltd. 2014 Equity Incentive Plan (the "2014 Plan"). The 2014 Plan authorizes the board of directors or a committee of the board to grant incentive share options, non-qualified share options, share appreciation rights, restricted awards, which include restricted shares and restricted share units ("RSUs"), and performance awards to eligible employees, consultants and directors of the Company. The Company accounts for grants to its board of directors as grants to employees.

As of December 31, 2020, 2,324,228 ordinary shares remained available for future grant under the 2014 Plan. In accordance with Nasdaq Listing Rule 5635(c)(4), the board of directors or a committee of the board may also issue inducement grants outside of the 2014 Plan, material to an individual's entering into employment with the Company.

Share option activity under the 2014 Plan is summarized as follows:

	Number of Shares	Weighted-Average Exercise Price	Weighted-Average Remaining Contractual Term (in years)	Aggregate Intrinsic Value (in thousands)(1)
Outstanding as of January 1, 2020	3,838,549	$ 19.54		
Granted	1,024,010	8.55		
Exercised	(288,270)	2.57		
Forfeited or cancelled	(700,894)	31.91		
Outstanding as of December 31, 2020	3,873,395	$ 15.67	5.63	$ 5,794
Options exercisable as of December 31, 2020	2,783,041	$ 16.37	4.58	$ 5,792

(1) The aggregate intrinsic value of options is calculated as the difference between the exercise price of the share options and the fair value of the Company's ordinary shares for those share options that had exercise prices lower than the fair value of the ordinary shares as of the end of the period.

Options generally vest over periods of one to four years, and options that are forfeited or cancelled are available to be granted again. The contractual life of options is generally five or ten years from the grant date. Of the options granted in 2020, 103,000 options were granted outside of the 2014 Plan, as inducement grants material to certain individuals entering into employment with the Company.

The assumptions used in the Black-Scholes option pricing model to determine the fair value of share options granted to employees during the period were as follows:

	For the Year Ended December 31,	
	2020	2019
Risk-free interest rate	0.19% – 0.84%	1.34% – 2.62%
Expected term (in years)	3.0 – 6.1	3.0 – 6.1
Expected volatility	69% – 74%	68% – 74%
Expected dividend yield	0%	0%

There were no options granted to non-employees during the years ended December 31, 2020 and 2019.

RSU activity for the year ended December 31, 2020 is summarized as follows:

	RSUs	Average Grant Date Fair Value (in dollars per share)
Outstanding as of January 1, 2020	1,751,862	$ 41.81
Granted	77,125	9.17
Vested	(208,123)	39.98
Forfeited	(440,649)	37.59
RSUs Outstanding at December 31, 2020	1,180,215	$ 41.57

RSUs that are forfeited are available to be granted again. Of the RSUs outstanding at December 31, 2020, 452,194 are time-based RSUs and 728,021 are performance-based RSUs. Time-based RSUs generally vest over periods of one to four years. Vesting of the performance-based RSUs is contingent on the occurrence of certain regulatory or commercial milestones. The Company did not recognize expense in 2020 or 2019 related to the performance-based RSUs as the related milestones were not considered probable of achievement. Of the RSUs granted in 2020, 27,000 were granted outside of the 2014 Plan, as inducement grants material to certain individuals entering into employment with the Company.

As of December 31, 2020, the unrecognized compensation cost related to outstanding options was $7.2 million. The unrecognized compensation cost related to outstanding options is expected to be recognized over a weighted-average period of approximately 1.5 years. For the years ended December 31, 2020 and 2019, the weighted-average grant date fair value per granted option was $5.07 and $11.95, respectively. The aggregate fair value of options that vested during the years ended December 31, 2020 and 2019 was $9.6 million and $15.2 million, respectively. The unrecognized compensation costs related to outstanding time-based RSUs was $10.7 million as of December 31, 2020, and is expected to be recognized over a weighted-average period of approximately 2.0 years. The total fair value of RSUs vested during the years ended December 31, 2020 and 2019 was $1.6 million and $4.2 million, respectively.

Employee Share Purchase Plan

The Wave Life Sciences Ltd. Employee Share Purchase Plan (“ESPP”) allows all full-time and certain part-time employees to purchase the Company’s ordinary shares at a discount to fair market value. Eligible employees may enroll in a six-month offering period beginning every January 15th and July 15th. Shares are purchased at a price equal to 85% of the lower of the fair market value of the Company’s ordinary shares on the first business day or the last business day of an offering period. Eligible employees who elected to participate in the ESPP were able to participate in the ESPP for the first time beginning on January 15, 2020. During the year ended December 31, 2020, 25,239 ordinary shares were issued under the ESPP. As of December 31, 2020, there were 974,761 ordinary shares available for issuance under the ESPP.

Share-based compensation expense for the years ended December 31, 2020 and 2019 is classified as operating expenses in the consolidated statements of operations and comprehensive loss as follows:

	For the Year Ended December 31,	
	2020	2019
	(in thousands)	
Research and development expenses	$ 6,779	$ 9,479
General and administrative expenses	7,517	10,030
Total share-based compensation expense	$ 14,296	$ 19,509

8. LEASES

Lease Arrangements

The Company enters into lease arrangements for its facilities. A summary of the arrangements is as follows:

Operating Leases

On September 26, 2016, and as amended on December 31, 2016, the Company entered into a 10 year and 9 month lease, which includes two successive five-year renewal options, for its facility in Lexington, Massachusetts, which the Company uses primarily for its current good manufacturing practices ("cGMP") manufacturing, as well as for additional laboratory and office space. Throughout the term of the lease, the Company is responsible for paying certain costs and expenses, in addition to the rent, as specified in the lease, including a proportionate share of applicable taxes, operating expenses and utilities. As required under the terms of the lease agreement, the Company has placed restricted cash of approximately $2.7 million and $2.6 million in a separate bank account as of December 31, 2020 and 2019, respectively.

As of December 31, 2018, the Company had received $11.4 million of tenant improvement allowances, which was the maximum amount allowed per the lease for the Lexington, Massachusetts facility. In applying the ASC 842 transition guidance, the Company utilized the operating lease classification and recorded a lease liability and a right-of-use asset on the ASC 842 effective date, with the lease incentive obligation being de-recognized and serving to reduce the right-of-use asset.

In April 2015, the Company entered into a lease agreement for an office and laboratory facility in Cambridge, Massachusetts (the "Cambridge Lease"), which commenced in October 2015 with a term of 7.5 years with a five-year renewal option to extend the lease. As required under the terms of the lease agreement, the Company has placed restricted cash of $1.0 million in a separate bank account as of December 31, 2020 and 2019. In applying the ASC 842 transition guidance, the Company utilized the operating lease classification and recorded lease liability and a right-of-use asset on the ASC 842 effective date.

In December 2020, the Company exercised its option under the Cambridge Lease to lease the additional office and laboratory space at the existing facility. The combined space will constitute the entire building. The lease for the additional space is expected to commence on October 1, 2021 with a term of five years. Future minimum lease payments related to this non-cancelable operating lease for the additional space total $5.4 million, of which $0.3 million is related to payments in 2021 and $5.1 million is related to payments beyond 2021. As the lease term for the additional space has not yet commenced, the Company has not yet recognized rent expense for the additional space and the future minimum lease payments are not included in the table below. On the commencement date of the lease of the additional space in 2021, the Company will record a right-of-use asset and corresponding operating lease liability on its consolidated balance sheets and begin recognizing straight-line rent expense under ASC 842. The Company has not made any payments to date related to this lease of the additional space.

The following table contains a summary of the lease costs recognized under ASC 842 and other information pertaining to the Company's operating leases for the year ended December 31, 2020:

	For the Year Ended December 31,	
	2020	2019
	(in thousands)	
Lease cost		
Operating lease cost	$ 4,472	$ 4,472
Total lease cost	$ 4,472	$ 4,472
Other information		
Operating cash flows used for operating leases	$ 5,846	$ 5,675
Operating lease liabilities arising from obtaining right-of-use assets	$ —	$ —
Weighted average remaining lease term	6.4 years	7.3 years
Weighted average discount rate	8.5%	8.5%

Future minimum lease payments under the Company's non-cancelable operating leases as of December 31, 2020, are as follows:

	As of December 31, 2020
	(in thousands)
2021	6,021
2022	6,201
2023	5,236
2024	5,002
2025	5,152
Thereafter	10,773
Total lease payments	$ 38,385
Less: imputed interest	(9,080)
Total operating lease liabilities	$ 29,305

9. COMMITMENTS AND CONTINGENCIES

Unasserted Claims

In the ordinary course of business, the Company may be subject to legal proceedings, claims and litigation as the Company operates in an industry susceptible to patent and other legal claims. The Company accounts for estimated losses with respect to legal proceedings and claims when such losses are probable and estimable. Legal costs associated with these matters are expensed when incurred. The Company is not currently a party to any material legal proceedings.

10. NET LOSS PER ORDINARY SHARE

Basic loss per share is computed by dividing net loss attributable to ordinary shareholders by the weighted-average number of ordinary shares outstanding:

	Year Ended December 31,	
	2020	2019
	(in thousands except share and per share data)	
Numerator:		
Net loss attributable to ordinary shareholders	$ (149,910)	$ (193,638)
Denominator:		
Weighted-average ordinary shares outstanding	39,227,618	33,866,487
Net loss per share, basic and diluted	$ (3.82)	$ (5.72)

The Company's potentially dilutive shares, which include outstanding share options to purchase ordinary shares and restricted share units, are considered to be ordinary share equivalents and are only included in the calculation of diluted net loss per share when their effect is dilutive.

The following potential ordinary shares, presented based on amounts outstanding at each period end, were excluded from the calculation of diluted net loss per share attributable to ordinary shareholders for the periods indicated because including them would have had an anti-dilutive effect:

	As of December 31,	
	2020	2019
Options to purchase ordinary shares	3,873,395	3,838,549
RSUs	1,180,215	1,751,862
Series A preferred shares	3,901,348	3,901,348

11. INCOME TAXES

The components of loss before income taxes were as follows:

	Year Ended December 31,	
	2020	2019
	(in thousands)	
Singapore	$ (9,931)	$ (5,931)
Rest of world	(140,820)	(187,707)
Loss before income taxes	$ (150,751)	$ (193,638)

During the year ended December 31, 2020, the Company recorded an income tax benefit of $0.8 million, which was primarily due to the release of a portion of the Company's uncertain tax positions as a result of a lapse in the statute of limitations. During the year ended December 31, 2019, the Company recorded no income tax benefit or provision.

During the year ended December 31, 2020, the Company recorded no income tax benefit for the net operating losses incurred in Singapore and the United Kingdom, due to uncertainty regarding future taxable income in those jurisdictions. During the year ended December 31, 2019, the Company recorded no income tax benefit for the net operating losses incurred in Singapore, the United States, and the United Kingdom, due to uncertainty regarding future taxable income in those jurisdictions. In May 2016, the Company established a wholly-owned subsidiary in Ireland, however no income tax expense or benefit has been recorded during the years ended December 31, 2020 or 2019.

The components of the benefit (provision), net for income taxes were as follows:

	Year Ended December 31,	
	2020	2019
	(in thousands)	
Current benefit (provision), net for income taxes:		
Singapore	$ —	$ —
Rest of world	841	—
Total current benefit (provision), net for income taxes	$ 841	$ —
Deferred benefit (provision), net for income taxes:		
Singapore	$ —	$ —
Rest of world	—	—
Total deferred benefit (provision), net for income taxes	$ —	$ —
Total benefit (provision), net for income taxes	$ 841	$ —

A reconciliation of the Singapore statutory income tax rate to the Company's effective income tax rate is as follows:

	Year Ended December 31,	
	2020	2019
Singapore statutory income tax rate	17.0%	17.0%
Federal and state tax credits	5.4	9.4
Permanent differences	(2.4)	(1.5)
Changes in reserves for uncertain tax positions	(1.3)	(3.2)
Foreign rate differential	6.1	7.0
Tax rate change	2.6	(0.4)
Other	(1.2)	1.3
Change in deferred tax asset valuation allowance	(25.6)	(29.6)
Effective income tax rate	0.6%	—

The components of the Company's deferred tax assets and liabilities as of December 31, 2020 and 2019 are as follows:

	December 31,	
	2020	2019
	(in thousands)	
Deferred tax assets:		
Net operating loss carryforwards	$ 133,841	$ 89,585
Federal and state tax credits	36,151	31,336
Share-based compensation	5,880	6,342
Accumulated amortization	962	11,169
Operating lease liabilities	8,006	8,892
Deferred revenue	13,956	14,299
Other	1,146	424
Total deferred tax assets	199,942	162,047
Valuation allowance	(195,381)	(156,680)
Net deferred tax assets	4,561	5,367
Deferred tax liabilities:		
Operating lease right-of-use assets	(4,435)	(4,945)
Accumulated depreciation	(117)	(422)
Other	(9)	—
Total deferred tax liabilities	(4,561)	(5,367)
Net deferred tax assets (liabilities)	$ —	$ —

A roll-forward of the valuation allowance for the years ended December 31, 2020 and 2019 is as follows:

	Year Ended December 31,	
	2020	2019
	(in thousands)	
Balance at beginning of year	$ 156,680	$ 99,438
Increase in valuation allowance	38,653	57,235
Effect of foreign currency translation	48	7
Balance at end of year	$ 195,381	$ 156,680

As of December 31, 2020, the Company had federal net operating loss carryforwards in the United States of $213.5 million, $211.5 million of which may be available to offset future income tax liabilities indefinitely, while $2.0 million of carryforwards that were in existence as of December 31, 2017 may offset future income tax liabilities up through 2037. As of December 31, 2020, the Company had state net operating loss carryforwards of $206.0 million that will begin to expire in 2038. As of December 31, 2020 and 2019, the Company had U.S. federal research and development tax credit carryforwards of approximately $10.3 million and $8.9 million, respectively, available to offset future U.S. federal income taxes and will begin to expire in 2031. As of December 31, 2020 and 2019, the Company had state research and development tax credit carryforwards of approximately $7.4 million and $6.3 million, respectively, available to offset future state income taxes and will begin to expire in 2033, and state investment tax credit carryforwards of $0.7 million and $1.1 million, respectively, that will begin to expire in 2021. As of December 31, 2020, the Company had a U.S. orphan drug credit carryforward of $19.4 million that will begin to expire in 2037.

As of December 31, 2020 and 2019, the Company had net operating loss carryforwards in Japan of $3.0 million and $2.9 million, respectively, which may be available to offset future income tax liabilities and begin to expire in 2023.

As of December 31, 2020 and 2019, the Company had net operating loss carryforwards in Singapore of $179.3 million and $171.6 million, respectively, which may be available to offset future income tax liabilities and can be carried forward indefinitely.

As of December 31, 2020 and 2019, the Company had net operating loss carryforwards in the United Kingdom of $233.3 million and $133.1 million, which may be available to offset future income tax liabilities and can be carried forward indefinitely.

The Company has evaluated the positive and negative evidence bearing upon its ability to realize its deferred tax assets. As of December 31, 2020, management has considered the Company's history of cumulative net losses incurred since inception and its lack of commercialization of any products or generation of any revenue from product sales since inception and has concluded that it is more likely than not that the Company will not realize the benefits of the deferred tax assets in all jurisdictions. Accordingly, a full valuation allowance has been established against those deferred tax assets as of December 31, 2020.

The valuation allowance increased by approximately $38.7 million in 2020 and $57.2 million in 2019 primarily as a result of operating losses generated with no corresponding financial statement benefit. The Company may release this valuation allowance when management determines that it is more-likely-than-not that the deferred tax assets will be realized. Any release of valuation allowance will be recorded as a tax benefit either increasing net income or decreasing net loss.

The Company's reserves related to taxes and its accounting for uncertain tax positions are based on a determination of whether and how much of a tax benefit taken by the Company in its tax filings or positions is more-likely-than-not to be realized following resolution of any potential contingencies present related to the tax benefit.

A summary of activity in the Company's unrecognized tax benefits is as follows:

	2020	2019
	(in thousands)	
Unrecognized tax benefit at the beginning of the year	$ 16,682	$ 10,219
Tax positions related to prior years	(310)	(14)
Tax positions related to statute lapse	(313)	(23)
Tax positions related to the current year	2,357	6,500
Unrecognized tax benefit at the end of the year	$ 18,416	$ 16,682

As of December 31, 2020 and 2019, the total amount of gross unrecognized tax benefits, which excludes interest and penalties, was $18.4 million and $16.7 million, respectively. At December 31, 2020, $0.2 million of the net unrecognized tax benefits would affect the Company's annual effective tax rate if recognized.

The Company anticipates that $0.2 million of the total unrecognized tax benefits at December 31, 2020 will decrease within the next twelve months due to a statute lapse.

The Company's policy is to record interest and penalties related to uncertain tax positions as part of its income tax provision. As of December 31, 2020 and 2019, the Company had recorded less than $0.1 million of interest or penalties related to uncertain tax positions.

The Company files income tax returns as prescribed by the tax laws of the jurisdictions in which it operates. In the normal course of business, the Company is subject to examination by various tax authorities in the United States, Japan, Singapore and the United Kingdom. Tax years from 2016 to the present are still open to examination in the United States, from 2016 to the present in Japan, from 2016 to the present in Singapore and from 2018 to the present in the United Kingdom. To the extent that the Company has tax attribute carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by the tax authorities to the extent utilized in a future period.

As of December 31, 2020 and 2019, $61.0 million and $17.2 million, respectively, of cash was held by the subsidiaries outside of Singapore. The Company does not provide for Singapore income tax or foreign withholding taxes on foreign unrepatriated earnings, as the Company intends to permanently reinvest undistributed earnings in its foreign subsidiaries. If the Company decides to change this assertion in the future to repatriate any additional foreign earnings, the Company may be required to accrue and pay taxes. Because of the complexity of Singapore and foreign tax rules applicable to the distribution of earnings from foreign subsidiaries to Singapore, the determination of the unrecognized deferred tax liability on these earnings is not practicable.

Utilization of the net operating loss carryforwards and research and development tax credit carryforwards in the United States may be subject to a substantial annual limitation under Section 382 of the Internal Revenue Code of 1986, as amended (the "Code"), due to ownership changes that have occurred previously or that could occur in the future. These ownership changes may limit the amount of carryforwards that can be utilized annually to offset future taxable income. In general, an ownership change, as defined by Section 382, results from transactions increasing the ownership of certain shareholders or public groups in the shares of a corporation by more than 50% over a three-year period. In 2018, the Company completed a study to assess whether an ownership change has occurred or whether there have been multiple ownership changes since its formation. The results of this study indicated that the Company experienced ownership changes as defined by Section 382 of the Code. Based on the results of the study, management has determined that the limitations will not have a material impact on the Company's ability to utilize its net operating losses and research and development credit carryforwards to offset future tax liabilities. Should an ownership change have occurred after December 31, 2018 or occur in the future, the Company's ability to utilize its net operating losses and research and development tax credit carryforwards may be limited.

12. EMPLOYEE BENEFIT PLANS

The Company has a 401(k) retirement and savings plan (the "401(k) Plan") covering employees of Wave USA. The 401(k) Plan allows employees to make contributions up to the maximum allowable amount set by the Internal Revenue Service. Under the 401(k) Plan, the Company may make discretionary contributions as approved by the board of directors. The Company made contributions of $0.9 million and $1.0 million in the years ended December 31, 2020 and 2019, respectively.

13. RELATED PARTIES

The Company had the following related party transactions for the periods presented in the accompanying consolidated financial statements:

- In 2012, the Company entered into a consulting agreement for scientific advisory services with Dr. Gregory L. Verdine, one of the Company's founders and a member of the Company's board of directors. The consulting agreement does not have a specific term and may be terminated by either party upon 14 days' prior written notice. Pursuant to the consulting agreement, the Company pays Dr. Verdine approximately $13 thousand per month, plus reimbursement for certain expenses.

733 CONCORD AVENUE
CAMBRIDGE, MASSACHUSETTS
(the "**Building**")

FIRST AMENDMENT
("**First Amendment**")

EXECUTION DATE:	December 9, 2020
LANDLORD:	CPI/King 733 Concord Owner, LLC, a Delaware limited liability company (as successor-in-interest to King 733 Concord LLC, a Delaware limited liability company)
TENANT:	Wave Life Sciences USA, Inc., a Delaware corporation
EXISTING PREMISES:	Approximately 30,893 rentable square feet of space in the Building (the "**Existing Premises**"), as more particularly described in the Existing Lease (as defined below).
ROFO PREMISES:	Approximately 13,126 rentable square feet of space on the first (1st) floor of the Building, identified as "Premises" as shown on the plan attached hereto as Exhibit 1D. The parties stipulate that the Rentable Square Footage of the ROFO Premises is correct and shall not be remeasured.
DATE OF EXISTING LEASE:	April 6, 2015

BACKGROUND

WHEREAS, by letter dated October 13, 2020 (the "**Offer**"), Landlord provided Tenant with Landlord's Offer for the ROFO Premises in accordance with Exhibit 12 of the above-described lease (as amended, the "**Existing Lease**"), which Offer for the ROFO Premises Tenant accepted on October 16, 2020.

WHEREAS, Landlord and Tenant desire to amend the Existing Lease to reflect, among other provisions, the expansion of the Premises to include the ROFO Premises, upon the terms and conditions hereinafter set forth.

NOW, THEREFORE, the Existing Lease is hereby amended as follows (the Existing Lease, as amended by this First Amendment, shall hereafter be referred to as the "**Lease**"). Any

capitalized terms used herein shall have the same definition as set forth in the Existing Lease, except to the extent otherwise set forth in this First Amendment.

1. ROFO Premises

a. Demise of ROFO Premises. Landlord hereby demises and leases to Tenant, and Tenant hereby hires and takes from Landlord, the ROFO Premises. Said demise of the ROFO Premises shall be for a term commencing on the ROFO Premises Commencement Date (as hereinafter defined) and expiring on the last day of the sixtieth (60th) full calendar month after the ROFO Premises Commencement Date (the "**ROFO Premises Expiration Date**"). Except as set forth herein, said demise of the ROFO Premises shall be upon all of the terms and conditions set forth in the Lease (as amended by this First Amendment) applicable to the Existing Premises.

b. ROFO Premises Commencement Date.

i. The "**ROFO Premises Commencement Date**" shall be the date that is the later of: (A) the date that is three (3) days after Tenant's receipt of notice from Landlord of the expected ROFO Premises Commencement Date and (B) the date on which Landlord delivers possession of the ROFO Premises to Tenant with all base building systems and structural components serving the ROFO Premises (in each case, which Landlord is required to repair and maintain pursuant to and in accordance with the provisions of the Lease) in good working order and condition, but otherwise in "as-is" condition, broom clean (with all furniture, fixtures, equipment and other personal property removed therefrom), vacant, and free and clear of any occupants; it being agreed that the delivery of the ROFO Premises in such condition shall not detract from or limit Landlord's repair and maintenance obligations with respect to the Premises (including the ROFO Premises) under the Lease. Prior to the ROFO Premises Commencement Date, Landlord shall provide Tenant with a copy of the surrender plan (or substantial equivalent) of the current occupant of the ROFO Premises and reasonable evidence that the work required thereby has been (or will be) completed prior to the ROFO Premises Commencement Date. It is estimated that the ROFO Premises Commencement Date shall occur on or about October 1, 2021; but in no event shall the ROFO Premises Commencement Date occur prior to August 1, 2021. Landlord shall use diligent efforts to deliver the ROFO Premises to Tenant on or about October 1, 2021, however, the failure of Landlord to deliver the ROFO Premises to Tenant on or before October 1, 2021 shall in no way affect the validity of the Lease, this First Amendment, or the obligations of Tenant thereunder (except that the ROFO Premises Commencement Date shall not occur until the date Landlord delivers the ROFO Premises to Tenant in accordance with this paragraph), and Tenant shall not have any claim against Landlord and Landlord shall have no liability to Tenant by reason thereof. Notwithstanding the foregoing, if the ROFO Premises Commencement Date has not occurred on or before the ROFO Rent Credit Date (as hereinafter defined), then, as Tenant's sole and exclusive remedy on account thereof, Tenant shall be entitled to a rent credit against Tenant's obligation to pay Base Rent in respect of the ROFO Premises only equal to one (1) day for each day between the ROFO Rent Credit Date and the ROFO Premises Commencement Date. The "**ROFO Rent Credit Date**" shall mean December 31, 2021, as such date shall be extended due to any delay caused by an act or omission by Tenant and/or Tenant's agents, employees or contractors, Landlord's Force Majeure or any other delay that is beyond Landlord's reasonable control (it being agreed that, if the existing tenant of the ROFO Premises

has not timely vacated the ROFO Premises by the current expiration date of such tenant's lease, then so long as Landlord is using commercially reasonable efforts to deliver the ROFO Premises to Tenant vacant and free and clear of any occupants, such delay shall be considered to be "beyond Landlord's reasonable control" for purposes hereof).

ii. Tenant shall not have any right to occupy all or any part of the ROFO Premises for the Permitted Uses under the Lease prior to the ROFO Premises Commencement Date; provided, however that Landlord (or Landlord's property manager) shall exercise good faith efforts to accommodate Tenant's requests for occasional access to the ROFO Premises prior to the ROFO Premises Commencement Date for the limited purpose of viewing the same in connection with Tenant's planning for future occupancy, in all cases subject to any limitations or restrictions contained in the existing tenant's lease.

iii. When the ROFO Premises Commencement Date has occurred, such date and the ROFO Premises Expiration Date shall be evidenced by a document reasonably acceptable to both parties and executed by Landlord and Tenant and delivered each to the other, but the failure of Landlord or Tenant to execute or deliver such document shall have no effect upon such dates.

iv. Subject to subsection (i) above and Landlord's ongoing service, maintenance, repair, insurance and restoration obligations under the Lease, (a) all work which Tenant deems necessary to prepare the ROFO Premises for Tenant's use and occupancy and/or to refurbish the ROFO Premises shall be performed by Tenant at Tenant's sole cost and expense, in accordance with the provisions of the Lease, including, without limitation, Section 11 of the Lease and (b) Landlord has no obligation to perform any work, supply any materials, incur any expense or make any alterations or improvements to prepare the ROFO Premises for Tenant's occupancy.

v. Effective on the ROFO Premises Commencement Date and continuing until the earlier to occur of the expiration of the Term under the Existing Lease for the Existing Premises and the ROFO Premises Expiration Date, (A) all references in the Lease to "**Premises**" shall be deemed to mean the Existing Premises and the ROFO Premises, collectively, (B) the Premises shall then consist of a total of 44,019 rentable square feet, which the parties stipulate shall be the correct Rentable Square Footage of the Premises, which shall not be remeasured and which the parties acknowledge is the entirety of the interior leasable area of the Building, (C) Tenant's Share for the Premises shall be increased to 100%, (D) Tenant shall have the right to install and maintain signage on the exterior of the Building and on any monument serving the Building, and no third party shall have the right to maintain or install signage thereon (provided, however, that the foregoing shall not limit or restrict Landlord from installing Building identification signage on the Building or monument), (E) the number of Tenant's Parking Spaces shall be increased to one hundred twelve (112) surface parking spaces (the "**Full Building Parking Minimum**") located in the Parking Area more particularly identified in the plan attached hereto on Exhibit 2 and made a part hereof, and (F) in no event shall Landlord, in connection with the exercise of its rights under Section 2.2 of the Existing Lease, reduce the number of Tenant's Parking Spaces to less than the Full Building Parking Minimum.

vi. Notwithstanding anything in the Lease to the contrary, effective on the ROFO Premises Commencement Date and continuing until the earlier to occur of the expiration of the Term under the Existing Lease for the Existing Premises and the ROFO Premises Expiration

Date, if (A) Tenant removes the two (2) 3000 liter nitrogen tanks (the "**Nitrogen Tanks**") on the Property that were installed by Tenant in accordance with the provisions of the letter agreement dated September 28, 2016 from PPF OFF King 733 Concord Owner, LLC (Landlord's predecessor in interest) to Tenant (the "**Nitrogen Tank Letter**"), (B) such removal is performed in accordance with the provisions of the Nitrogen Tank Letter, and (C) Tenant restores the three (3) surface parking spaces in the Parking Area that were occupied by the Nitrogen Tanks so that they are usable parking spaces in the Parking Area (the "**Restored Parking Spaces**"), then Tenant's Parking Spaces shall be increased to one hundred fifteen (115) surface parking spaces located in the Parking Area and the Full Building Parking Minimum shall be increased to one hundred fifteen (115) surface parking spaces, in each case, to include the Restored Parking Spaces accordingly.

2. Rent – ROFO Premises.

a. Base Rent – ROFO Premises. From and after the ROFO Premises Commencement Date, Tenant shall pay Base Rent in respect of the ROFO Premises as set forth below.

Period of Time	Annual Base Rent	Monthly Base Rent
ROFO Premises Lease Year 1*	$ 1,017,265.00	$ 84,772.08
ROFO Premises Lease Year 2	$ 1,047,782.95	$ 87,315.25
ROFO Premises Lease Year 3	$ 1,079,216.44	$ 89,934.70
ROFO Premises Lease Year 4	$ 1,111,592.93	$ 92,632.74
ROFO Premises Lease Year 5	$ 1,144,940.72	$ 95,411.73

*Any twelve-(12)-month period commencing as of the ROFO Premises Commencement Date, or as of any anniversary of the ROFO Premises Commencement Date, except that if the ROFO Premises Commencement Date does not fall on the first day of a calendar month, then the first ROFO Premises Lease Year shall begin on the ROFO Premises Commencement Date, and end on the last day of the month containing the first anniversary of the ROFO Premises Commencement Date, and each succeeding ROFO Premises Lease Year shall begin on the day following the last day of the prior ROFO Premises Lease Year.

b. Additional Rent – ROFO Premises. Commencing as of the ROFO Premises Commencement Date, and continuing thereafter through the ROFO Premises Expiration Date, for and with respect to the ROFO Premises (i) Tenant shall pay Tenant's Share of Operating Costs to Landlord in accordance with the provisions of Section 5.2(c) of the Lease, (ii) Tenant shall pay Tenant's Share of Taxes to Landlord in accordance with the provisions of Section 5.3(c) of the Lease, and (iii) Tenant shall pay the cost of all utility services consumed in the ROFO Premises (including, without limitation, electricity, gas and water) in accordance with the provisions of Section 9 of the Lease.

c. Tenant's Share; Tenant's Parking Spaces; Tenant's Signage – ROFO Premises. From and after the ROFO Premises Commencement Date until the earlier of the Expiration Date under the Existing Lease for the Existing Premises and the ROFO Premises Expiration Date, Tenant's Share and Tenant's Parking Spaces with respect to the ROFO Premises and the Existing Premises, collectively, shall be as set forth in Section 1(b)(v) above. In the event that the

Expiration Date under the Existing Lease for the Existing Premises occurs prior to the ROFO Premises Expiration Date, then from and after the Expiration Date under the Existing Lease for the Existing Premises until the ROFO Premises Expiration Date, (i) Tenant's Share with respect to the ROFO Premises shall be 29.82%, (ii) Tenant's right to exclusive signage on the Building and any monument set forth in Section 1(b)(v)(D) shall be of no further force or effect, (iii) the number of Tenant's Parking Spaces set forth in Section 1(b)(v)(E) shall be decreased to thirty-four (34) surface parking spaces located in the Parking Area, and (iv) the Full Building Parking Minimum set forth in Section 1(b)(v)(F) shall be of no further force or effect.

3. Notice Addresses. For all purposes of the Lease, the Notice addresses for Landlord and Tenant set forth in Section 24 of the Lease is hereby deleted in its entirety, and the following address is substituted therefor:

If to Landlord:	CPI/King 733 Concord Owner, LLC c/o King Street Properties 800 Boylston Street, Suite 1570 Boston, MA 02199 Attention: Stephen D. Lynch
With copies to:	Goulston & Storrs PC 400 Atlantic Avenue Boston, MA 02110 Attention: King Street
If to Tenant:	Wave Life Sciences USA, Inc. 733 Concord Avenue Cambridge, MA 02138 Attention: Paul B. Bolno, Kyle Moran and Bryant Cook
	with a copy to:
	Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C. One Financial Center Boston, MA 02111 Attention: Stuart A. Offner, Esq.

4. Alterations; Restoration.

a. Landlord acknowledges that Tenant may elect to pursue certain Alterations as may be reasonably required to combine the Existing Premises and the ROFO Premises into a single, integrated premises; provided, however, that all such Alterations (if any) shall be performed by Tenant in accordance with the terms and conditions of the Lease applicable to Alterations, including, without limitation, Landlord's approval of such Alterations in accordance with the terms of the Existing Lease and Landlord's right to require the removal thereof pursuant to Sections 4(a) and 4(b) below.

b. Upon the Expiration Date under the Existing Lease or earlier termination of the Term under the Existing Lease for the Existing Premises, Tenant shall have no obligation to perform or pay for the removal of any Alterations or other improvements approved by Landlord and installed by or for Tenant in the Existing Premises or Building in connection with any such Alterations, except for (i) items previously identified by Landlord as to be removed by Tenant and (ii) Alterations whose removal is expressly required by Landlord at the time of Landlord's approval thereof (including, without limitation, any Alterations performed by Tenant pursuant to Section 4(a) above that Landlord expressly requires Tenant to remove at the time of Landlord's approval thereof).

c. Upon the ROFO Premises Expiration Date or earlier termination of the term as it relates to the ROFO Premises, Tenant shall have no obligation to perform or pay for the removal of any (i) Alterations or other improvements installed by or for Tenant in the ROFO Premises or Building in connection with such Alterations, except for any Alterations whose removal is expressly required by Landlord at the time of Landlord's approval thereof (including, without limitation, any Alterations performed by Tenant pursuant to Section 4(a) above that Landlord expressly requires Tenant to remove at the time of Landlord's approval thereof), and (ii) improvements, furniture, fixtures, equipment or cabling existing in the ROFO Premises on the ROFO Premises Commencement Date.

5. Miscellaneous

a. Notice of Lease. In accordance with Section 25.16 of the Existing Lease, at Tenant's option, each of the parties shall join in the execution, in recordable form and substantially similar to the form attached as Exhibit 10 to the Existing Lease, of a statutory notice of lease and/or written declaration, or an amendment to any existing notice and/or declaration, reflecting Tenant's lease of the ROFO Premises and the term thereof, which notice of lease may be recorded by Tenant with the Middlesex South Registry of Deeds and/or filed with the Registry District of the Land Court, as appropriate.

b. Broker. Tenant and Landlord each warrants and represents that it has dealt with no broker in connection with the consummation of this First Amendment other than Colliers International (the "**Broker**"). Tenant and Landlord each agrees to defend, indemnify and save the other harmless from and against any claims arising in breach of the representation and warranty set forth in the immediately preceding sentence. Landlord shall be solely responsible for the payment of any brokerage commission to Broker.

c. Deleted/Inapplicable Lease Provisions. Exhibit 12 (Right of First Offer) of the Lease is hereby deleted in its entirety and is of no further force and effect. Section 3 and Exhibit 3 of the Lease shall have no applicability with respect to this First Amendment.

d. Ratification. In all other respects, except as expressly modified herein, the Lease is hereby ratified and confirmed. The submission of drafts of this document for examination and negotiation does not constitute an offer, or a reservation of or option for any of the terms and conditions set forth in this First Amendment, and this First Amendment shall not be binding upon Landlord or Tenant unless and until Landlord shall have executed and delivered a fully executed copy of this First Amendment to Tenant, it being agreed that the foregoing shall not affect the

validity of Tenant's prior exercise of the Right of First Offer pursuant to the terms set forth in the Offer.

e. Conflict. In the event that any of the provisions of the Existing Lease are inconsistent with this First Amendment or the state of facts contemplated hereby, the provisions of this First Amendment shall control.

f. Counterparts. This First Amendment may be executed in any number of counterparts and by each of the undersigned on separate counterparts, which counterparts taken together shall constitute one and the same instrument. This First Amendment may be executed by electronic signature, which shall be considered as an original signature for all purposes and shall have the same force and effect as an original signature. Without limitation, in addition to electronically produced signatures, "electronic signature" shall include faxed versions of an original signature or electronically scanned and transmitted versions (e.g., via pdf) of an original signature.

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SIGNATURES ON FOLLOWING PAGE]

EXECUTED as of the date first above written.

LANDLORD:

CPI/KING 733 CONCORD OWNER, LLC,
a Delaware limited liability company

By: /s/ Michael Gershenson
Name: Michael Gershenson
Title: Authorized Signatory

TENANT:

WAVE LIFE SCIENCES USA, INC.
a Delaware corporation

By: /s/ Kyle Moran
Name: Kyle Moran
Title: SVP, Finance & Operations

EXHIBIT 1D
PLAN OF ROFO PREMISES

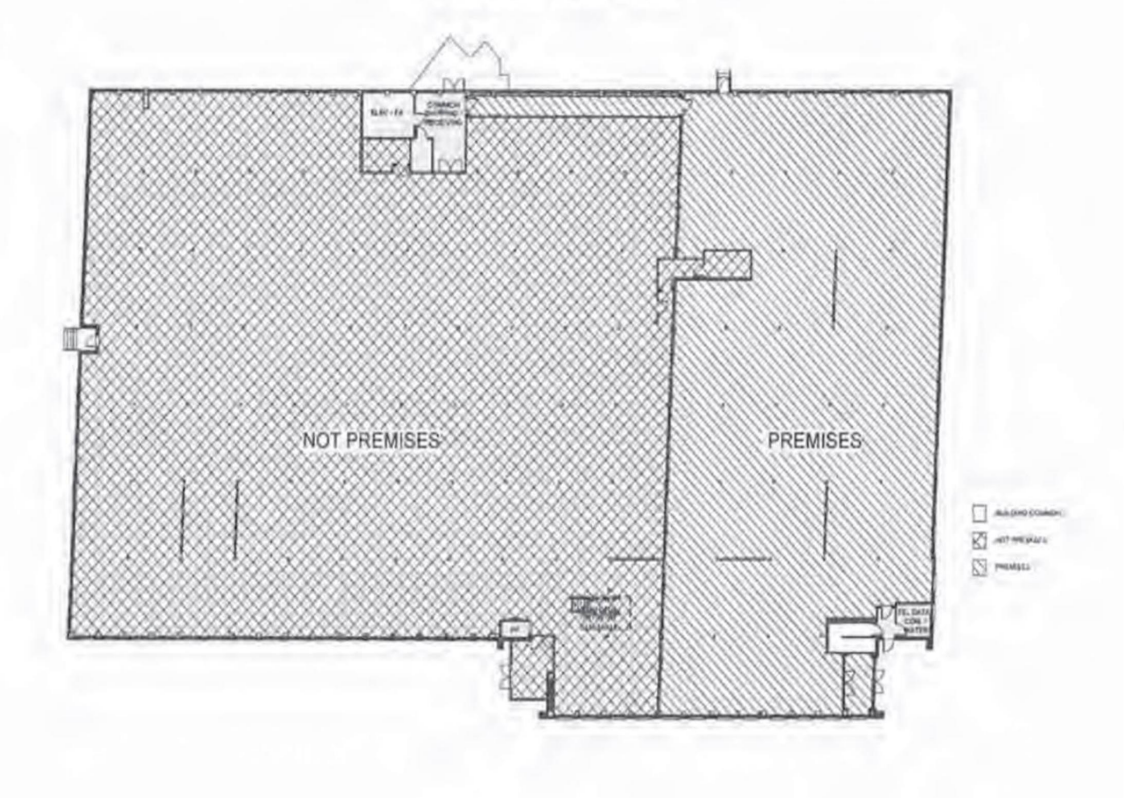

Exhibit 1D

EXHIBIT 2
PARKING AREA

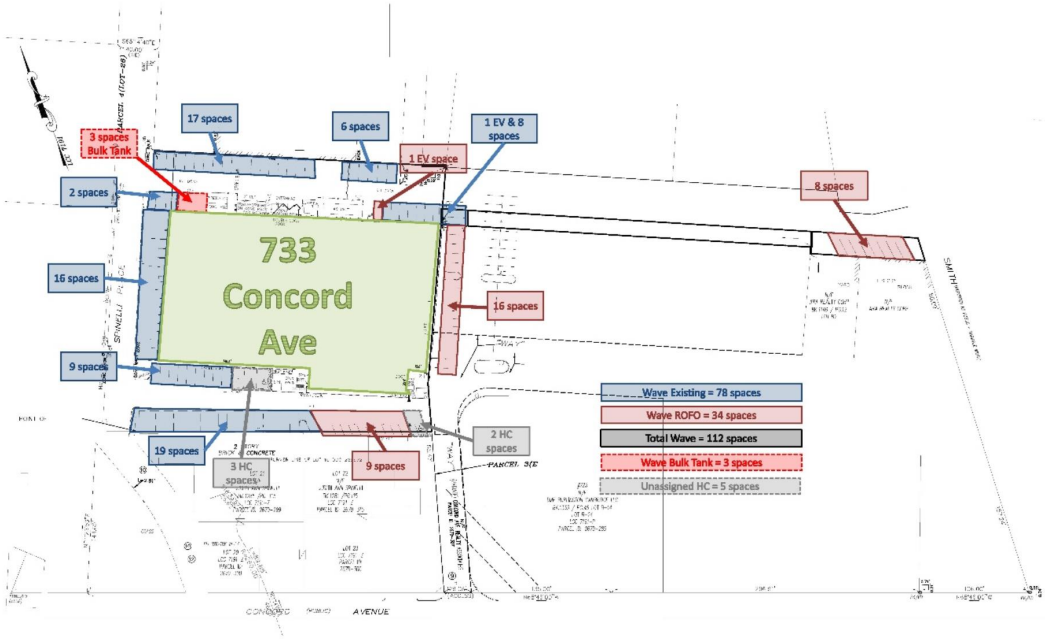

Exhibit 2

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

Wave Life Sciences Ltd. (the "Company," "we," "us" or "our") has one class of securities registered under Section 12 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"): our ordinary shares, no par value.

DESCRIPTION OF SHARE CAPITAL

General

The following description of our share capital and provisions of our constitution (formerly known as our memorandum and articles of association) are summaries and are qualified by reference to the Singapore Companies Act and our constitution. A copy of our constitution has been filed with the Securities and Exchange Commission as an exhibit to our Annual Report on Form 10-K of which this Exhibit is a part.

Ordinary Shares

As of December 31, 2020, our issued and paid-up ordinary share capital consists of 48,778,678 ordinary shares. We currently have only one class of issued ordinary shares, which have identical rights in all respects and rank equally with one another. Our ordinary shares have no par value and there is no authorized share capital under Singapore law. There is a provision in our constitution which provides that we may issue shares with such preferred, deferred or other special rights or such restrictions, whether in regard to dividend, voting, return of capital or otherwise as our board of directors may determine.

All of our shares presently issued are fully paid-up, and existing shareholders are not subject to any calls on these shares. Although Singapore law does not recognize the concept of "non-assessability" with respect to newly-issued shares, we note that any purchaser of our shares who has fully paid up all amounts due with respect to such shares will not be subject under Singapore law to any personal liability to contribute to the assets or liabilities of our company in such purchaser's capacity solely as a holder of such shares. We believe that this interpretation is substantively consistent with the concept of "non-assessability" under most, if not all, U.S. state corporations laws. All of our shares are in registered form. We cannot, except in the circumstances permitted by the Singapore Companies Act, grant any financial assistance for the acquisition or proposed acquisition of our own shares. Except as described below under "—Takeovers," there are no limitations imposed by the Singapore Companies Act or by our constitution on the right of shareholders not resident in Singapore to hold or vote ordinary shares.

Transfer Agent and Registrar

The transfer agent and registrar for our ordinary shares is Computershare Trust Company, N.A.

Nasdaq Global Market

Our ordinary shares are listed for quotation on The Nasdaq Global Market under the symbol "WVE."

New Shares

Under the Singapore Companies Act, new shares may be issued only with the prior approval of our shareholders in a general meeting. General approval may be sought from our shareholders in a general meeting for the issue of shares. Approval, if granted, will lapse at the earlier of:

- the conclusion of the next annual general meeting; or
- the expiration of the period within which the next annual general meeting is required by law to be held (i.e., within six months after the end of each financial year),

but any approval may be revoked or varied by the company in a general meeting.

Our shareholders have provided such general authority to issue new ordinary shares until the conclusion of our 2021 annual general meeting. Such approval will lapse in accordance with the preceding paragraph if our shareholders do not grant a new approval at our 2021 annual general meeting. Subject to this and the provisions of the Singapore Companies Act and our constitution, our board

of directors may allot and issue or grant options over or otherwise dispose of new ordinary shares to such persons on such terms and conditions and with the rights and restrictions as they may think fit to impose.

Preferred Shares

Series A Preferred Shares

As of December 31, 2020, we have 3,901,348 Series A preferred shares outstanding. These shares are currently held by one of our largest shareholders, Shin Nippon Biomedical Laboratories, Ltd. The terms of the Series A preferred shares as set out in our constitution include (1) no voting rights at any general meeting other than in limited circumstances, (2) a liquidation preference equal to $0.002 per Series A preferred share, (3) no entitlement to dividends and (4) the right to convert the Series A preferred shares at any time on a one-for-one basis into ordinary shares at the discretion of the holder in accordance with the constitution.

The holders of the Series A preferred shares are not entitled to vote at any general meeting. The only instances in which the holders of the Series A preferred shares are able to vote at a general meeting would be if (but only if) the matters to be discussed at the meeting relate to or there is intent to pass resolutions on (i) abrogating or changing the rights attached to the Series A preferred shares; and (ii) for the winding up of the Company. Such resolutions would require the unanimous approval of the holders of the Series A preferred shares.

Other Preferred Shares

Under the Singapore Companies Act, different classes of shares in a public company may be issued only if (a) the issue of the class or classes of shares is provided for in the constitution of the public company and (b) the constitution of the public company sets out in respect of each class of shares the rights attached to that class of shares. Our constitution provides that we may issue shares of a different class with preferred, deferred or other special rights, or such restrictions, whether in regard to dividend, voting, return of capital or otherwise as our board of directors may determine. Under Singapore law, our preferred shareholders will have the right to attend any general meeting and in a poll at such general meeting, to have at least one vote for every preferred share held:

- upon any resolution concerning the voluntary winding-up of our company under Section 160 of the Insolvency, Restructuring and Dissolution Act 2018 of Singapore (No. 40 of 2018);
- upon any resolution which varies the rights attached to such preferred shares; or
- in the case of preferred shares issued after August 15, 1984, but before the commencement of Section 96 of the Companies (Amendment) Act 2014, when the dividends to be paid on our preferred shares or any part thereof are more than twelve months in arrears and unpaid, for the period they remain in arrears and unpaid.

We may, subject to the Singapore Companies Act and the prior approval in a general meeting of our shareholders, issue preferred shares which are, or at our option or are to be, subject to redemption provided that such preferred shares may not be redeemed out of capital unless:

- all the directors have made a solvency statement in relation to such redemption; and
- we have lodged a copy of the statement with the Accounting and Corporate Regulatory Authority of Singapore.

Further, such shares must be fully paid-up before they are redeemed.

As of December 31, 2020, we have no preferred shares outstanding other than the Series A preferred shares described above and we have no plans to issue additional preferred shares.

Registration Rights under our Share Purchase Agreement with Pfizer

Under the terms of our Share Purchase Agreement dated as of May 5, 2016 with an affiliate of Pfizer Inc. (the “Pfizer Affiliate”), the Pfizer Affiliate agreed that the 1,875,000 ordinary shares that the Pfizer Affiliate purchased from us under the Share Purchase Agreement (the “Pfizer Shares”), would be subject to a lock-up restriction, such that the Pfizer Affiliate will not, and will also cause its affiliates not to, without our prior approval, sell, transfer or otherwise dispose of the Pfizer Shares until certain specified periods of time after the effective date of the Share Purchase Agreement. For a certain period following the expiration of the lock-up period, subject to certain conditions and limitations, we agreed to provide certain demand registration rights to the Pfizer Affiliate in order to register all or a portion of the Pfizer Shares purchased by the Pfizer Affiliate. We also provided the Pfizer Affiliate with certain “piggyback” registration rights for a certain period following the expiration of the lock-up period, subject to certain conditions and limitations, such that when we propose to register our ordinary shares for our account, the Pfizer Affiliate will have the right to

include some or all of the Pfizer Shares in such registration. The Share Purchase Agreement also contains other customary terms and conditions of the parties with respect to the registration of the Pfizer Shares.

Registration Rights under our Share Purchase Agreement with Takeda

On February 19, 2018, we entered into a share purchase agreement with Takeda Pharmaceutical Company Limited ("Takeda"), pursuant to which Takeda purchased 1,096,892 of our ordinary shares (the "Takeda Shares"). In connection with the share purchase agreement, Takeda and we agreed upon certain rights and restrictions as set forth in the Investor Agreement, dated as of April 2, 2018 (the "Investor Agreement"). The Takeda Shares would be subject to a lock-up restriction, such that Takeda will not, and will also cause its affiliates not to, without our prior approval, sell, transfer or otherwise dispose of the Takeda Shares until certain specified periods of time after the effective date of the Investor Agreement. For a certain period following the expiration of the lock-up period, subject to certain conditions and limitations, we agreed to provide certain demand registration rights to Takeda in order to register all or a portion of the Takeda Shares purchased by Takeda. We also provided Takeda with certain "piggyback" registration rights for a certain period following the expiration of the lock-up period, subject to certain conditions and limitations, such that when we propose to register our ordinary shares for our account, Takeda will have the right to include some or all of the Takeda Shares in such registration. The Investor Agreement also contains other customary terms and conditions of the parties with respect to the registration of Takeda Shares.

Transfer of Ordinary Shares

Subject to applicable securities laws in relevant jurisdictions and our constitution, our ordinary shares are freely transferable. Our constitution provides that shares may be transferred by a duly signed instrument of transfer in any usual or common form or in a form approved by the directors and Nasdaq. The directors may decline to register any transfer unless, among other things, evidence of payment of any stamp duty payable with respect to the transfer is provided together with other evidence of ownership and title as the directors may reasonably require to show the right of the transferor to make the transfer. We will replace lost or destroyed certificates for shares upon notice to us and upon, among other things, the applicant furnishing evidence and indemnity as the directors may require and the payment of all applicable fees.

Election and Re-election of Directors

We may, by ordinary resolution, remove any director before the expiration of his or her period of office, notwithstanding anything in our constitution or in any agreement between us and such director. We may also, by an ordinary resolution, appoint another person in place of a director removed from office pursuant to the foregoing.

Under our constitution, subject to the Singapore Companies Act, any director shall retire at the next annual general meeting and shall then be eligible for re-election at that meeting.

Our board of directors shall have the power, at any time and from time to time, to appoint any person to be a director either to fill a casual vacancy or as an additional director so long as the total number of directors shall not at any time exceed the maximum number (if any) fixed by or in accordance with our constitution.

Shareholders' Meetings

We are required to hold an annual general meeting each calendar year and within six months after the end of each financial year. The directors may convene an extraordinary general meeting whenever they think fit and they must do so upon the written request of shareholders holding not less than 10% of the total number of paid-up shares as of the date of deposit of the requisition carrying the right to vote at a general meeting. In addition, two or more shareholders holding not less than 10% of our total number of issued shares (excluding our treasury shares) may call a meeting of our shareholders.

The Singapore Companies Act provides that a shareholder is entitled to attend any general meeting and speak on any resolution put before the general meeting. Unless otherwise required by law or by our constitution, resolutions put forth at general meetings may be decided by ordinary resolution, requiring the affirmative vote of a majority of the shareholders present in person or represented by proxy at the meeting and entitled to vote on the resolution. An ordinary resolution suffices, for example, for appointments of directors. A special resolution, requiring an affirmative vote of not less than three-fourths of the shareholders present in person or represented by proxy at the meeting and entitled to vote on the resolution, is necessary for certain matters under Singapore law, such as an alteration of our constitution. A shareholder entitled to attend and vote at a meeting of the company, or at a meeting of any class of shareholders of the company, shall be entitled to appoint another person or persons, whether a shareholder of the company or not, as his proxy to attend and vote instead of the shareholder at the meeting. Under the Singapore Companies Act, a proxy appointed to attend and vote instead of the shareholder shall also have the same right as the shareholder to speak at the meeting, but unless the constitution of the

company otherwise provides, (i) a proxy shall not be entitled to vote except on a poll, (ii) a shareholder shall not be entitled to appoint more than two proxies to attend and vote at the same meeting and (iii) where a shareholder appoints two proxies the appointment shall be invalid unless the shareholder specifies the proportions of his holdings to be represented by each proxy.

Notwithstanding the foregoing, a registered shareholder entitled to attend and vote at a meeting of the company held pursuant to an order of court under Section 210(1) of the Singapore Companies Act, or at any adjourned meeting under Section 210(3) of the Singapore Companies Act, is, unless the court orders otherwise, entitled to appoint only one proxy to attend and vote at the same meeting, and except where the aforementioned applies, a registered shareholder having a share capital who is a relevant intermediary (as defined under the Singapore Companies Act) may appoint more than two proxies in relation to a meeting to exercise all or any of his rights to attend and to speak and vote at the meeting, but each proxy must be appointed to exercise the rights attached to a different share or shares held by him (which number and class of shares shall be specified), and at such meeting, the proxy has the right to vote on a show of hands.

Only registered shareholders of our company, and their proxies, will be entitled to attend, speak and vote at any meeting of shareholders. Under the Singapore Companies Act, public companies may issue non-voting shares and shares that confer special, limited or conditional voting rights, such that the holder of a share may vote on a resolution before a general meeting of the company if, in accordance with the provisions of Section 64A of the Singapore Companies Act, the share confers on the holder a right to vote on that resolution.

Voting Rights

As provided under our constitution and the Singapore Companies Act, voting at any meeting of shareholders is by show of hands unless a poll has been demanded prior to the declaration of the result of the show of hands by, among others, (i) the chairman or (ii) at least one shareholder present in person or by proxy or by attorney or, in the case of a corporation, by a representative entitled to vote thereat, in each case representing in the aggregate not less than 5% of the total voting rights of all shareholders having the right to vote at the general meeting, provided that no poll shall be demanded in respect of an election of a chairman or relating to any adjournment of such meeting. On a poll every shareholder who is present in person or by proxy or by attorney, or in the case of a corporation, by a representative, has one vote for every share held by such shareholder. Proxies need not be shareholders.

Only those shareholders who are registered in our register of members as holders of ordinary shares will be entitled to vote at any meeting of shareholders. Therefore, DTC, or its nominee, will grant an omnibus proxy to DTC participants holding our shares in book-entry form through a broker, bank, nominee, or other institution that is a direct or indirect participant in the DTC. Such shareholders will have the right to instruct their broker, bank, nominee or other institution holding these shares on how to vote such shares by completing the voting instruction form provided by the applicable broker, bank, nominee, or other institution. Whether voting is by a show of hands or by a poll, DTC's vote will be voted by the chairman of the meeting according to the results of the DTC's participants' votes (which results will reflect the instructions received from shareholders that own our shares electronically in book-entry form).

Minority Rights

The rights of minority shareholders of Singapore companies are protected, among other things, under Section 216 of the Singapore Companies Act, which gives the Singapore courts a general power to make any order, upon application by any shareholder of a company, as they think fit to remedy any of the following situations:

- the affairs of a company are being conducted or the powers of the board of directors are being exercised in a manner oppressive to, or in disregard of the interests of, one or more of the shareholders, including the applicant; or
- a company takes an action, or threatens to take an action, or the shareholders pass a resolution, or propose to pass a resolution, which unfairly discriminates against, or is otherwise prejudicial to, one or more of the shareholders, including the applicant.

Singapore courts have wide discretion as to the remedy they may grant, and the remedies listed in the Singapore Companies Act itself are not exclusive. In general, Singapore courts may, with a view to bringing to an end or remedying the matters complained of:

- direct or prohibit any act or cancel or modify any transaction or resolution;
- regulate the conduct of the affairs of the company in the future;
- authorize civil proceedings to be brought in the name of, or on behalf of, the company by a person or persons and on such terms as the court may direct;
- provide for the purchase of a minority shareholder's shares by the other shareholders or by the company itself;

- in the case of a purchase of shares by the company provide for a reduction accordingly of the company's capital; or
- provide that the company be wound up.

Dividends

Subject to any preferential rights of holders of any outstanding preferred shares, holders of our ordinary shares will be entitled to receive dividends and other distributions in cash, shares or property as may be declared by our company from time to time. We may, by ordinary resolution, declare dividends at a general meeting of shareholders, but we are restricted from paying dividends in excess of the amount recommended by our board of directors. Pursuant to Singapore law and our constitution, no dividend may be paid except out of our profits. To date, we have not declared any cash dividends on our ordinary shares and have no current plans to pay cash dividends in the foreseeable future.

Bonus and Rights Issues

In a general meeting, our shareholders may, upon the recommendation of the directors, capitalize any reserves or profits and distribute them as bonus shares, credited as paid-up, to the shareholders in proportion to their shareholdings.

Subject to the provisions of the Singapore Companies Act and our constitution, our directors may also issue rights to take up additional ordinary shares to our shareholders in proportion to their respective ownership. Such rights are subject to any condition attached to such issue and the regulations of any stock exchange on which our shares are listed, as well as U.S. federal and blue sky securities laws applicable to such issue.

Takeovers

The Singapore Code on Take-overs and Mergers applies to, among other things, the acquisition of voting shares of Singapore-incorporated listed public companies or unlisted public companies with more than 50 shareholders and net tangible assets of S$5 million or more. Any person acquiring, whether by a series of transactions over a period of time or not, either on his or her own or together with parties acting in concert with such person, 30% or more of our voting shares, or, if such person holds, either on his or her own or together with parties acting in concert with such person, between 30% and 50% (both amounts inclusive) of our voting shares, and if such person (or parties acting in concert with such person) acquires additional voting shares representing more than 1% of our voting shares in any six-month period, must, except with the consent of the Securities Industry Council in Singapore, extend a mandatory takeover offer for the remaining voting shares in accordance with the provisions of the Singapore Code on Take-overs and Mergers. Responsibility for ensuring compliance with the Singapore Code on Take-overs and Mergers rests with parties (including company directors) to a take-over or merger and their advisors.

"Parties acting in concert" comprise individuals or companies who, pursuant to an agreement or understanding (whether formal or informal), cooperate, through the acquisition by any of them of shares in a company, to obtain or consolidate effective control of that company. Certain persons are presumed (unless the presumption is rebutted) to be acting in concert with each other. They are as follows:

- a company, its parent company, subsidiaries and fellow subsidiaries, the associated companies of any of the company and its related companies, subsidiaries and fellow subsidiaries, companies whose associated companies include any of these companies and any person who has provided financial assistance (other than a bank in the ordinary course of business) to any of the foregoing for the purchase of voting rights;
- a company with any of its directors (together with their close relatives, related trusts and companies controlled by any of the directors, their close relatives and related trusts);
- a company with any of its pension funds and employee share schemes;
- a person with any investment company, unit trust or other fund whose investment such person manages on a discretionary basis, but only in respect of the investment account which such person manages;
- a financial or other professional advisor, including a stockbroker, with its client in respect of the shareholdings of the advisor and persons controlling, controlled by or under the same control as the advisor;
- directors of a company (together with their close relatives, related trusts and companies controlled by any of such directors, their close relatives and related trusts) which is subject to an offer or where the directors have reason to believe a bona fide offer for their company may be imminent;

- partners; and
- an individual and (i) such person's close relatives, (ii) such person's related trusts, (iii) any person who is accustomed to act in accordance with such person's instructions, (iv) companies controlled by the individual, such person's close relatives, related trusts or any person who is accustomed to act in accordance with such person's instructions and (v) any person who has provided financial assistance (other than a bank in the ordinary course of business) to any of the foregoing for the purchase of voting rights.

Subject to certain exceptions, a mandatory offer must be in cash or be accompanied by a cash alternative at not less than the highest price paid by the offeror or parties acting in concert with the offeror during the offer period and within the six months prior to its commencement.

Under the Singapore Code on Take-overs and Mergers, where effective control of a company is acquired or consolidated by a person, or persons acting in concert, a general offer to all other shareholders is normally required. An offeror must treat all shareholders of the same class in an offeree company equally. A fundamental requirement is that shareholders in the company subject to the takeover offer must be given sufficient information, advice and time to consider and decide on the offer. These legal requirements may impede or delay a takeover of our company by a third-party.

We may submit an application to the Securities Industry Council of Singapore for a waiver from the Singapore Code on Take-overs and Mergers so that the Singapore Code on Take-overs and Mergers will not apply to our company for so long as we are not listed on a securities exchange in Singapore. We will make an appropriate announcement if we submit the application and when the result of the application is known.

Liquidation or Other Return of Capital

On a winding-up or other return of capital, subject to any special rights attaching to the Series A preferred shares or to any other class of shares, holders of ordinary shares will be entitled to participate in any surplus assets in proportion to their shareholdings.

COMPARISON OF SHAREHOLDER RIGHTS

We are incorporated under the laws of Singapore. The following discussion summarizes material differences between the rights of holders of our ordinary shares and the rights of holders of the common stock of a typical corporation incorporated under the laws of the state of Delaware which result from differences in governing documents and the laws of Singapore and Delaware.

This discussion does not purport to be a complete statement of the rights of holders of our ordinary shares under applicable law in Singapore and our constitution or the rights of holders of the common stock of a typical corporation under applicable Delaware law and a typical certificate of incorporation and bylaws.

Delaware	Singapore
Board of Directors	
A typical certificate of incorporation and bylaws provides that the number of directors on the board of directors will be fixed from time to time by a vote of the majority of the authorized directors. Under Delaware law, a board of directors can be divided into classes and cumulative voting in the election of directors is only permitted if expressly authorized in a corporation's certificate of incorporation.	The constitution of companies will typically state the minimum and maximum number of directors as well as provide that the number of directors may be increased or reduced by shareholders via ordinary resolution passed at a general meeting, provided that the number of directors following such increase or reduction is within the maximum (if any) and minimum number of directors provided in our constitution and the Singapore Companies Act, respectively.
Limitation on Personal Liability of Directors	
A typical certificate of incorporation provides for the elimination of personal monetary liability of directors for breach of fiduciary duties as directors to the fullest extent permissible under the laws of Delaware, except for liability (i) for any breach of a director's loyalty to the corporation or its stockholders, (ii) for acts or omissions not in good faith or which involve intentional misconduct or a knowing violation of law, (iii) under Section 174 of the Delaware General Corporation Law (relating to the liability of directors for unlawful payment of a dividend or an unlawful stock purchase or redemption) or (iv) for any transaction from which the director derived an improper personal benefit. A typical certificate of incorporation also provides that if the Delaware General Corporation Law is amended so as to allow further elimination of, or limitations on, director liability, then the liability of directors will be eliminated or limited to the fullest extent permitted by the Delaware General Corporation Law as so amended.	Pursuant to the Singapore Companies Act, any provision (whether in the constitution, a contract with the company or otherwise) exempting or indemnifying a director against any liability which by law would otherwise attach to him or her in respect of any negligence, default, breach of duty or breach of trust of which such director may be guilty in relation to the company is void. However, a company is not prohibited from (a) purchasing and maintaining for any such director insurance against any such liability, or (b) indemnifying such director against any liability incurred by him or her to a person other than the company except when the indemnity is against any liability (i) of the director to pay a fine in criminal proceedings, (ii) of the director to pay a penalty in respect of non-compliance with any regulatory requirements, (iii) incurred by the director in defending criminal proceedings in which he or she is convicted, (iv) incurred by the director in defending civil proceedings brought by the company or a related company in which judgment is given against him or her, or (v) incurred by the director in connection with an application for relief under Section 76A(13) or Section 391 of the Singapore Companies Act in which the court refuses to grant him or her relief. Nevertheless, a director can be released by the shareholders of a company for breaches of duty to a company except in the case of fraud, illegality, insolvency of the company and oppression or disregard of minority interests. Subject to the Singapore Companies Act and every other Singapore statute for the time being in force and affecting the Company, we may indemnify our directors against costs, charges, fees, and other expenses that may be incurred by any of them in defending any proceedings (whether civil or criminal) relating to anything done or omitted or alleged to be done or omitted by such person acting in his or her capacity as a director of our company, in which judgment is given in his or her favor, or in which he or she is acquitted or in which the courts have granted relief pursuant to the provisions of the Singapore Companies Act, provided that such indemnity shall not extend to any liability which by law would otherwise attach to him or her in respect of any negligence, default, breach of duty or breach of trust of which he may be guilty in relation to our company, or which would otherwise result in such indemnity being voided under applicable Singapore laws.

Delaware	Singapore
Interested Shareholders	
Section 203 of the Delaware General Corporation Law generally prohibits a Delaware corporation from engaging in specified corporate transactions (such as mergers, stock and asset sales, and loans) with an "interested stockholder" for three years following the time that the stockholder becomes an interested stockholder. Subject to specified exceptions, an "interested stockholder" is a person or group that owns 15% or more of the corporation's outstanding voting stock (including any rights to acquire stock pursuant to an option, warrant, agreement, arrangement or understanding, or upon the exercise of conversion or exchange rights, and stock with respect to which the person has voting rights only), or is an affiliate or associate of the corporation and was the owner of 15% or more of the voting stock at any time within the previous three years. A Delaware corporation may elect to "opt out" of, and not be governed by, Section 203 through a provision in either its original certificate of incorporation, or an amendment to its original certificate or bylaws that was approved by majority stockholder vote. With a limited exception, this amendment would not become effective until 12 months following its adoption.	There are no comparable provisions under the Singapore Companies Act with respect to public companies which are not listed on the Singapore Exchange Securities Trading Limited.
Removal of Directors	
A typical certificate of incorporation and bylaws provide that, subject to the rights of holders of any preferred stock, directors may be removed at any time by the affirmative vote of the holders of at least a majority, or in some instances a supermajority, of the voting power of all of the then outstanding shares entitled to vote generally in the election of directors, voting together as a single class. A certificate of incorporation could also provide that such a right is only exercisable when a director is being removed for cause (removal of a director only for cause is the default rule in the case of a classified board).	Under the Singapore Companies Act, directors of a public company may be removed before expiration of their term of office, notwithstanding anything in its constitution or in any agreement between the public company and such directors, by ordinary resolution (i.e., a resolution which is passed by a simple majority of those shareholders present and voting in person or by proxy). Notice of the intention to move such a resolution has to be given to the company not less than 28 days before the meeting at which it is moved. The company shall then give notice of such resolution to its shareholders not less than 14 days before the meeting. Where any director removed in this manner was appointed to represent the interests of any particular class of shareholders or debenture holders, the resolution to remove such director will not take effect until such director's successor has been appointed.
Filling Vacancies on the Board of Directors	
A typical certificate of incorporation and bylaws provide that, subject to the rights of the holders of any preferred stock, any vacancy, whether arising through death, resignation, retirement, disqualification, removal, an increase in the number of directors or any other reason, may be filled by a majority vote of the remaining directors, even if such directors remaining in office constitute less than a quorum, or by the sole remaining director. Any newly elected director usually holds office for the remainder of the full term expiring at the annual meeting of stockholders at which the term of the class of directors to which the newly elected director has been elected expires.	The constitution of a Singapore company typically provides that the directors have the power to appoint any person to be a director, either to fill a vacancy or as an addition to the existing directors, but so that the total number of directors shall not at any time exceed the maximum number (if any) fixed by or in accordance with the constitution. Any director so appointed shall hold office until the next following annual general meeting, where such director will then be eligible for re-election. Our constitution provides that the directors may appoint any person to be a director either to fill a casual vacancy or as an additional director but so that the total number of Directors shall not at any time exceed the maximum number fixed by or in accordance with the constitution.

Delaware	Singapore
Amendment of Governing Documents	
Under the Delaware General Corporation Law, amendments to a corporation's certificate of incorporation require the approval of stockholders holding a majority of the outstanding shares entitled to vote on the amendment. If a class vote on the amendment is required by the Delaware General Corporation Law, a majority of the outstanding stock of the class is required, unless a greater proportion is specified in the certificate of incorporation or by other provisions of the Delaware General Corporation Law. Under the Delaware General Corporation Law, the board of directors may amend bylaws if so authorized in the charter. The stockholders of a Delaware corporation also have the power to amend bylaws.	Our constitution may be altered by special resolution (i.e., a resolution passed by at least a three-fourths majority of the shareholders entitled to vote, present in person or by proxy at a meeting for which not less than 21 days' written notice is given). The board of directors has no right to amend the constitution. Under the Singapore Companies Act, an entrenching provision may be included in the constitution with which a company is formed and may at any time be inserted into the constitution of a company only if all the shareholders of the company agree. An entrenching provision is a provision of the constitution of a company to the effect that other specified provisions of the constitution may not be altered in the manner provided by the Singapore Companies Act or may not be so altered except (i) by a resolution passed by a specified majority greater than 75% (the minimum majority required by the Singapore Companies Act for a special resolution) or (ii) where other specified conditions are met. The Singapore Companies Act provides that such entrenching provision may be removed or altered only if all the members of the company agree.
Meetings of Shareholders	
Annual and Special Meetings Typical bylaws provide that annual meetings of stockholders are to be held on a date and at a time fixed by the board of directors. Under the Delaware General Corporation Law, a special meeting of stockholders may be called by the board of directors or by any other person authorized to do so in the certificate of incorporation or the bylaws.	*Annual General Meetings* All companies are required to hold an annual general meeting after the end of each financial year within either 4 months (in the case of a public company that is listed on an exchange in Singapore approved by the Monetary Authority of Singapore) or 6 months (in the case of any other company). *Extraordinary General Meetings* Any general meeting other than the annual general meeting is called an "extraordinary general meeting." Notwithstanding anything in the constitution, directors of a company are required to convene an extraordinary general meeting if required to do so by requisition (i.e. written notice, requiring that a meeting be called, given to the directors) by shareholder(s) holding not less than 10% of the total number of paid-up shares as at the date of the deposit of the requisition carrying the right of voting at general meetings of the company. In addition, the constitution usually also provides that general meetings may be convened in accordance with the Singapore Companies Act by the directors.

Delaware	Singapore
Quorum Requirements	*Quorum Requirements*
Under the Delaware General Corporation Law, a corporation's certificate of incorporation or bylaws can specify the number of shares which constitute the quorum required to conduct business at a meeting, provided that in no event shall a quorum consist of less than one-third of the shares entitled to vote at a meeting.	Our constitution provides that any two shareholders present in person or by proxy or by attorney or, in the case of a corporation, by a representative and entitled to vote thereat; in each case representing in aggregate not less than a majority of the total voting rights of all shareholders having the right to vote at a general meeting, shall constitute a quorum. In the event a quorum is not present, the meeting if not convened on the requisition of shareholders may be adjourned for one week. When reconvened, the quorum for the meeting will be the same and if at such adjourned meeting a quorum is not present, the meeting will be dissolved.
	Shareholders' Rights at Meetings
	The Singapore Companies Act provides that every member shall, notwithstanding any provision in the constitution, have a right to attend any general meeting of the company and to speak on any resolution before the meeting. The company's constitution may provide that a member shall not be entitled to vote unless all calls or other sums personally payable by him in respect of shares in the company have been paid. Public companies may issue non-voting shares and shares that confer special, limited and conditional voting rights, such that the holder of a share may vote on a resolution before a general meeting if, in accordance with the provisions of Section 64A of the Singapore Companies Act, the share confers on the holder a right to vote on the resolution.
	Circulation of Shareholders' Resolutions
	Under the Singapore Companies Act, (a) any number of shareholders representing not less than 5% of the total voting rights of all the shareholders having at the date of requisition a right to vote at a meeting to which the requisition relates or (b) not less than 100 shareholders holding shares on which there has been paid up an average sum, per shareholder, of not less than S$500, may requisition the company to give to shareholders notice of any resolution which may properly be moved and is intended to be moved at the next annual general meeting, and circulate to shareholders any statement of not more than 1,000 words with respect to the matter referred to in any proposed resolution or the business to be dealt with at that meeting.
Indemnification of Officers, Directors and Employees	
Under the Delaware General Corporation Law, subject to specified limitations in the case of derivative suits brought by a corporation's stockholders in its name, a corporation may indemnify any person who is made a party to any third-party action, suit or proceeding on account of being a director, officer, employee or agent of the corporation (or was serving at the request of the corporation in such capacity for another corporation, partnership, joint venture, trust or other enterprise) against expenses, including attorney's fees, judgments, fines and amounts paid in settlement actually and reasonably incurred by him or her in connection with the action, suit or proceeding through, among other things, a majority vote of a quorum consisting of directors who were not parties to the suit or proceeding, if the person: • acted in good faith and in a manner he or she reasonably believed to be in or not opposed to the best interests of the corporation or, in some circumstances, at least not opposed to its best interests; and • in a criminal proceeding, had no reasonable cause to believe his or her conduct was unlawful. Delaware corporate law permits indemnification by a corporation under similar circumstances for expenses (including attorneys' fees) actually and reasonably incurred by such persons in connection with the defense or settlement of a derivative action or suit, except that no indemnification may be made in respect of any claim, issue or matter as to which the person is adjudged to be liable to the corporation unless the Delaware Court of Chancery or the court in which the action or suit was brought determines upon application that the person is fairly and reasonably entitled to indemnity for the expenses which the court deems to be proper.	Under Section 172 of the Singapore Companies Act, any provision exempting or indemnifying the officers of a company (including directors) against liability, which by law would otherwise attach to them in connection with any negligence, default, breach of duty or breach of trust in relation to the company is void. However, the Singapore Companies Act allows a company to: • purchase and maintain for any officer insurance against any liability which by law would otherwise attach to such officer in connection with any negligence, default, breach of duty or breach of trust in relation to the company; • indemnify such officer against any liability incurred by him or her to a person other than the company except when the indemnity is against any liability (i) of the officer to pay a fine in criminal proceedings, (ii) of the officer to pay a penalty in respect of non-compliance with any regulatory requirements, (iii) incurred by the officer in defending criminal proceedings in which he or she is convicted, (iv) incurred by the officer in defending civil proceedings brought by the company or a related company in which judgment is given against him or her, or (v) incurred by the officer in connection with an application for relief under Section 76A(13) or Section 391 of the Singapore Companies Act in which the court refuses to grant him or her relief. In cases where a director is sued by the company, the Singapore Companies Act gives the court the power to relieve directors either wholly or partially from their liability for their negligence, default, breach of duty or breach of trust. In order for relief to be obtained, it must be shown that (i) the director acted reasonably and honestly; and (ii) it is fair, having regard to all the

To the extent a director, officer, employee or agent is successful in the defense of such an action, suit or proceeding, the corporation is required by Delaware corporate law to indemnify such person for reasonable expenses incurred thereby. Expenses (including attorneys' fees) incurred by such persons in defending any action, suit or proceeding may be paid in advance of the final disposition of such action, suit or proceeding upon receipt of an undertaking by or on behalf of that person to repay the amount if it is ultimately determined that that person is not entitled to be so indemnified.

circumstances of the case including those connected with such director's appointment, to excuse the director. However, Singapore case law has indicated that such relief will not be granted to a director who has benefited as a result of his or her breach of trust.

Our constitution provides that subject to the provisions of the Singapore Companies Act and every other applicable statute for the time being in force concerning companies and affecting the company, the directors and officers are entitled to be indemnified against costs, charges, fees and other expenses that may be incurred by such person in defending any proceedings, whether civil or criminal, which relates to anything done or omitted or alleged to be done or omitted by such person as a director, officer or employee of the company and in which judgment is given in his or her favor or in which such person is acquitted or in which the courts have granted relief pursuant to the provisions of the Singapore Companies Act, provided that such indemnity shall not extend to any liability which by law would otherwise attach to him or her in respect of any negligence, default, breach of duty or breach of trust of which he or she may be guilty in relation to the company, or which would otherwise result in such indemnity being voided under applicable Singapore laws.

Delaware	Singapore
Shareholder Approval of Issuances of Shares	
Under Delaware law, the board of directors has the authority to issue, from time to time, capital stock in its sole discretion, as long the number the shares to be issued, together with those shares that are already issued and outstanding and those shares reserved to be issued, do not exceed the authorized capital for the corporation as previously approved by the stockholders and set forth in the corporation's certificate of incorporation. Under the foregoing circumstances, no additional stockholder approval is required for the issuance of capital stock. Under Delaware law, stockholder approval is required (i) for any amendment to the corporation's certificate of incorporation to increase the authorized capital and (ii) for the issuance of stock in a direct merger transaction where the number of shares exceeds 20% of the corporation's shares outstanding prior to the transaction, regardless of whether there sufficient authorized capital.	Section 161 of the Singapore Companies Act provides that notwithstanding anything in the company's constitution, the directors shall not exercise any power to issue shares without prior approval of Company's shareholders in a general meeting. The affirmative vote of shareholders holding at least a majority of the ordinary shares held by the shareholders present in person or represented by proxy at the annual general meeting and entitled to vote is required for this authorization. Once this shareholders' approval is obtained, unless previously revoked or varied by the company in general meeting, it continues in force until the conclusion of the next annual general meeting or the expiration of the period within which the next annual general meeting after that date is required by law to be held, whichever is earlier; but any approval may be revoked or varied by the company in general meeting. Notwithstanding this general authorization to allot and issue our ordinary shares, Wave will be required to seek shareholder approval with respect to future issuances of ordinary shares, where required under the Nasdaq Stock Market rules, such as if we were to propose an issuance of ordinary shares that would result in a change in control of Wave or in connection with a transaction involving the issuance of ordinary shares representing 20% or more of our outstanding ordinary shares.

Delaware	Singapore
Shareholder Approval of Business Combinations	
Generally, under the Delaware General Corporation Law, completion of a merger, consolidation, or the sale, lease or exchange of substantially all of a corporation's assets or dissolution requires approval by the board of directors and by a majority (unless the certificate of incorporation requires a higher percentage) of outstanding stock of the corporation entitled to vote. The Delaware General Corporation Law also requires a special vote of stockholders in connection with a business combination with an "interested stockholder" as defined in section 203 of the Delaware General Corporation Law. See "—Interested Shareholders" above.	The Singapore Companies Act and the Insolvency, Restructuring and Dissolution Act 2018 of Singapore (No. 40 of 2018) mandates that specified corporate actions require approval by the shareholders in a general meeting, notably: • notwithstanding anything in the company's constitution, directors are not permitted to carry into effect any proposals for disposing of the whole or substantially the whole of the company's undertaking or property unless those proposals have been approved by shareholders in a general meeting; • the company may by special resolution resolve that it be wound up voluntarily; • subject to the constitution of each amalgamating company, an amalgamation proposal must be approved by the shareholders of each amalgamating company via special resolution at a general meeting; • a compromise or arrangement proposed between a company and its shareholders, or any class of them, must, among other things, be approved by a majority in number representing three-fourths in value of the shareholders or class of shareholders present and voting either in person or by proxy at the meeting ordered by the court; and • notwithstanding anything in the company's constitution, the directors may not, without the prior approval of shareholders, issue shares, including shares being issued in connection with corporate actions.
Shareholder Action Without A Meeting	
Under the Delaware General Corporation Law, unless otherwise provided in a corporation's certificate of incorporation, any action that may be taken at a meeting of stockholders may be taken without a meeting, without prior notice and without a vote if the holders of outstanding stock, having not less than the minimum number of votes that would be necessary to authorize such action, consent in writing. It is not uncommon for a corporation's certificate of incorporation to prohibit such action.	There are no equivalent provisions under the Singapore Companies Act in respect of public companies which are listed on a securities exchange, like our company.

Shareholder Suits

Under the Delaware General Corporation Law, a stockholder may bring a derivative action on behalf of the corporation to enforce the rights of the corporation. An individual also may commence a class action suit on behalf of himself or herself and other similarly situated stockholders where the requirements for maintaining a class action under the Delaware General Corporation Law have been met. A person may institute and maintain such a suit only if such person was a stockholder at the time of the transaction which is the subject of the suit or his or her shares thereafter devolved upon him or her by operation of law. Additionally, under Delaware case law, the plaintiff generally must be a stockholder not only at the time of the transaction which is the subject of the suit, but also through the duration of the derivative suit. The Delaware General Corporation Law also requires that the derivative plaintiff make a demand on the directors of the corporation to assert the corporate claim before the suit may be prosecuted by the derivative plaintiff, unless such demand would be futile.

Standing

Only registered shareholders of our company reflected in our register of members are recognized under Singapore law as shareholders of our company. As a result, only registered shareholders have legal standing to institute shareholder actions against us or otherwise seek to enforce their rights as shareholders. Holders of book-entry interests in our shares will be required to exchange their book-entry interests for certificated shares and to be registered as shareholders in our shareholder register in order to institute or enforce any legal proceedings or claims against us, our directors or our executive officers relating to shareholder rights. A holder of book-entry interests may become a registered shareholder of our company by exchanging its interest in our shares for certificated shares and being registered in our shareholder register.

Personal remedies in cases of oppression or injustice

A shareholder may apply to the court for an order under Section 216 of the Singapore Companies Act to remedy situations where (i) the company's affairs are being conducted or the powers of the company's directors are being exercised in a manner oppressive to, or in disregard of the interests of one or more of the shareholders or holders of debentures of the company, including the applicant; or (ii) the company has done an act, or threatens to do an act, or the shareholders or holders of debentures have passed some resolution, which unfairly discriminates against, or is otherwise prejudicial to, one or more of the company's shareholders or holders of debentures, including the applicant.

Singapore courts have wide discretion as to the relief they may grant under such application, including, *inter alia*, directing or prohibiting any act or cancelling or varying any transaction or resolution, providing that the company be wound up, or authorizing civil proceedings to be brought in the name of or on behalf of the company by such person or persons and on such terms as the court directs.

Derivative actions and arbitrations

The Singapore Companies Act has a provision which provides a mechanism enabling shareholders to apply to the court for leave to bring a derivative action or commence an arbitration on behalf of the company. Derivative actions are also allowed as a common law action.

Applications are generally made by shareholders of the company, but courts are given the discretion to allow such persons as they deem proper to apply (e.g., beneficial owner of shares).

It should be noted that this provision of the Singapore Companies Act is primarily used by minority shareholders to bring an action or arbitration in the name and on behalf of the company or intervene in an action or arbitration to which the company is a party for the purpose of prosecuting, defending or discontinuing the action or arbitration on behalf of the company. Prior to commencing a derivative action or arbitration, the court must be satisfied that (i) 14 days' notice has been given to the directors of the company of the party's intention to commence such action or arbitration if the directors of the company do not bring, diligently prosecute or defend or discontinue the action, (ii) the party is acting in good faith and (iii) it appears to be prima facie in the interests of the company that the action be brought, prosecuted, defended or discontinued.

Class actions

The concept of class action suits in the United States, which allows individual shareholders to bring an action seeking to represent the class or classes of shareholders, does not exist in the same manner in Singapore. In Singapore, it is possible as a matter of procedure for a number of shareholders to begin proceedings on behalf of themselves and other shareholders who have the same interest in the proceedings whom they represent. These shareholders are known as "representative plaintiffs."

Delaware	Singapore
Distributions and Dividends; Repurchases and Redemptions	
The Delaware General Corporation Law permits a corporation to declare and pay dividends out of statutory surplus or, if there is no surplus, out of net profits for the fiscal year in which the dividend is declared and/or for the preceding fiscal year as long as the amount of capital of the corporation following the declaration and payment of the dividend is not less than the aggregate amount of the capital represented by the issued and outstanding stock of all classes having a preference upon the distribution of assets.	The Singapore Companies Act provides that no dividends can be paid to shareholders except out of profits. The Singapore Companies Act does not provide a definition on when profits are deemed to be available for the purpose of paying dividends and this is accordingly governed by case law. Our constitution provides that no dividend can be paid otherwise than out of profits.
Under the Delaware General Corporation Law, any corporation may purchase or redeem its own shares, except that generally it may not purchase or redeem these shares if the capital of the corporation is impaired at the time or would become impaired as a result of the redemption. A corporation may, however, purchase or redeem out of capital shares that are entitled upon any distribution of its assets to a preference over another class or series of its shares if the shares are to be retired and the capital reduced.	*Acquisition of a company's own shares* The Singapore Companies Act generally prohibits a company from acquiring its own shares or purporting to acquire the shares of its holding company or ultimate holding company, whether directly or indirectly, in any way, subject to certain exceptions. Any contract or transaction made or entered into in contravention of the aforementioned prohibition by which a company acquires or purports to acquire its own shares or shares in its holding company or ultimate holding company is void. However, provided that it is expressly permitted to do so by its constitution and subject to the special conditions of each permitted acquisition contained in the Singapore Companies Act, a company may: • redeem redeemable preferred shares on such terms and in such manner as is provided by its constitution. Preferred shares may be redeemed out of capital only if all the directors make a solvency statement in relation to such redemption in accordance with the Singapore Companies Act, and the company lodges a copy of the statement with the Registrar of Companies; • whether listed on an exchange in Singapore approved by the Monetary Authority of Singapore or any securities exchange outside Singapore, or not, make an off-market purchase of its own shares in accordance with an equal access scheme authorized in advance at a general meeting; • make a selective off-market purchase of its own shares in accordance with an agreement authorized in advance at a general meeting by a special resolution where persons whose shares are to be acquired and their associated persons have abstained from voting; and • whether listed on an exchange in Singapore approved by the Monetary Authority of Singapore or any securities exchange outside Singapore, or not, make an acquisition of its own shares under a contingent purchase contract which has been authorized in advance at a general meeting by a special resolution. A company may also purchase its own shares by an order of a Singapore court. • The total number of ordinary shares, stocks in any class and non-redeemable preferred shares that may be acquired by a company in a relevant period may not exceed 20% (or such other prescribed percentage) of the total number of ordinary shares, stocks in any class or non-redeemable preferred shares (as the case may be) as of the date of the resolution to acquire the shares. Where, however, a company has reduced its share capital by a special resolution or a Singapore court made an order to such effect, the total number of ordinary shares, stocks in any class or non-redeemable preferred shares shall be taken to be the total number of ordinary shares, stocks in any class or non-redeemable preferred shares (as the case may be) as altered by the special resolution or the order of the court. Payment, including any expenses (including brokerage or commission) incurred directly in the acquisition by the company of its own shares, may be made out of the company's profits or capital, provided that the company is solvent. *Financial assistance for the acquisition of shares* A public company or a company whose holding company or ultimate holding company is a public company may not give financial assistance to

any person whether directly or indirectly for the purpose of or in connection with:

- the acquisition or proposed acquisition of shares in the company or units of such shares; or
- the acquisition or proposed acquisition of shares in its holding company or ultimate holding company, or units of such shares.

Financial assistance may take the form of a loan, the giving of a guarantee, the provision of security, the release of an obligation, the release of a debt or otherwise.

However, it should be noted that a company may provide financial assistance for the acquisition of its shares or shares in its holding company or ultimate holding company if it complies with the requirements (including approval by special resolution) set out in the Singapore Companies Act.

Our constitution provides that subject to the provisions of the Singapore Companies Act, we may purchase or otherwise acquire our own shares upon such terms and subject to such conditions as we may deem fit. We may deal with any such shares which is so purchased or acquired by us in such manner as may be permitted under the Singapore Companies Act (including, without limitation, hold such shares as treasury shares).

Delaware	Singapore
Transactions with Officers or Directors	
Under the Delaware General Corporation Law, some contracts or transactions in which one or more of a corporation's directors has an interest are not void or voidable because of such interest provided that some conditions, such as obtaining the required approval and fulfilling the requirements of good faith and full disclosure, are met. Under the Delaware General Corporation Law, either (a) the stockholders or the board of directors of a corporation must approve in good faith any such contract or transaction after full disclosure of the material facts or (b) the contract or transaction must have been "fair" as to the corporation at the time it was approved. If board approval is sought, the contract or transaction must be approved in good faith by a majority of disinterested directors after full disclosure of material facts, even though less than a majority of a quorum.	Under the Singapore Companies Act, directors and the chief executive officer of the company are not prohibited from dealing with the company, but where they have an interest, whether directly or indirectly, in a transaction with the company, that interest must be disclosed to the board of directors. In particular, every director or chief executive officer who is in any way, whether directly or indirectly, interested in a transaction or proposed transaction with the company must, as soon as is practicable after the relevant facts have come to such director's or, as the case may be, the chief executive officer's knowledge, declare the nature of such interest at a meeting of the directors or send a written notice to the company detailing the nature, character and extent of the interest. In addition, a director or chief executive officer who holds any office or possesses any property which directly or indirectly might create interests in conflict with such director's or, as the case may be, the chief executive officer's duties as director or chief executive officer is required to declare the fact and the nature, character and extent of the conflict at a meeting of directors or send a written notice to the company detailing the nature, character and extent of the conflict. The Singapore Companies Act extends the scope of this statutory duty of a director and chief executive officer to disclose any interests by pronouncing that an interest of a member of a director's or, as the case may be, the chief executive officer's family (including spouse, son, adopted son, step-son, daughter, adopted daughter and step-daughter) will be treated as an interest of the director or chief executive officer (as the case may be). A director or chief executive officer shall not be deemed to be interested or at any time interested in a transaction or proposed transaction where the interest of the director or chief executive officer (as the case may be) consists only of being a member or creditor of a corporation which is interested in the transaction or proposed transaction with the company if the interest may properly be regarded as immaterial. Where the transaction or the proposed transaction relates to any loan to the company, no disclosure need be made where the director or chief executive officer (as the case may be) has only guaranteed the repayment of such loan, unless the constitution provides otherwise. Further, where the transaction or the proposed transaction has been or will be made with or for the benefit of a related corporation (i.e., the holding company, subsidiary or subsidiary of a common holding company), the director or chief executive officer shall not be deemed to be interested or at any time interested in such transaction or proposed transaction by virtue of only being a director or chief executive officer (as the case may be) of the related corporation, unless the constitution provides otherwise. Subject to specified exceptions, the Singapore Companies Act prohibits a company (other than an exempt private company) from, among others, (i) making a loan or a quasi-loan to its directors or to directors of a related corporation, or giving a guarantee or security in connection with such a loan or quasi-loan, (ii) entering into a credit transaction as creditor for the benefit of its directors or the directors of a related corporation, or giving a guarantee or any security in connection with such a credit transaction, (iii) arranging an assignment to or assumption by us of any rights, obligations or liabilities under a transaction which, if it had been entered into by us, would have been a restricted transaction, and (iv) taking part in an arrangement under which another person enters into a transaction which, if entered into by us, would have been a restricted transaction and such person obtains a benefit from us or our related corporation pursuant thereto. Companies are also prohibited from entering into any of these transactions with the spouse or children (whether adopted or natural or step-children) of its directors. Subject to specified exceptions, the Singapore Companies Act prohibits a company (other than an exempt private company) from making a loan or a quasi-loan to another company or a limited liability partnership or entering into any guarantee or providing any security in connection with a loan or a quasi-loan made to another company or a limited liability partnership by a person other than the first-mentioned company, entering into a credit transaction as a creditor for the benefit of another company or a limited liability partnership, or entering into any guarantee or provide any security

in connection with a credit transaction entered into by any person for the benefit of another company or a limited liability partnership if a director or directors of the first-mentioned company is or together are interested in 20% or more of the total voting power in the other company or the limited liability partnership (as the case may be).

Such prohibition shall extend to apply to a loan, quasi-loan, credit transaction made by a company (other than an exempt private company), a credit transaction made by a company (other than an exempt private company) for the benefit of another company or limited liability partnership and a guarantee or security provided by a company (other than an exempt private company) in connection with a loan or quasi-loan made by a person other than the first-mentioned company to another company or a limited liability partnership where such other company or limited liability partnership is incorporated or formed (as the case may be) outside Singapore, if a director or directors of the first-mentioned company (a) is or together are interested in 20% or more of the total voting power in the other company or limited liability partnership or (b) in a case where the other company does not have a share capital, exercises or together exercise control over the other company whether by reason of having the power to appoint directors or otherwise.

The Singapore Companies Act also provides that an interest of a member of a director’s family (including spouse, son, adopted son, step-son, daughter, adopted daughter and step-daughter) will be treated as an interest of the director.

Delaware	Singapore
Dissenters' Rights	
Under the Delaware General Corporation Law, a stockholder of a corporation participating in some types of major corporate transactions may, under varying circumstances, be entitled to appraisal rights pursuant to which the stockholder may receive cash in the amount of the fair market value of his or her shares in lieu of the consideration he or she would otherwise receive in the transaction.	There are no equivalent provisions in Singapore under the Singapore Companies Act.
Cumulative Voting	
Under the Delaware General Corporation Law, a corporation may adopt in its bylaws that its directors shall be elected by cumulative voting. When directors are elected by cumulative voting, a stockholder has the number of votes equal to the number of shares held by such stockholder times the number of directors nominated for election. The stockholder may cast all of such votes for one director or among the directors in any proportion.	There are no equivalent provisions in Singapore under the Singapore Companies Act.

Exhibit 10.15

EXECUTIVE EMPLOYMENT AGREEMENT

This Employment Agreement (the "Agreement"), made and entered into as of January 1, 2021, by and between Wave Life Sciences USA, Inc., a Delaware corporation ("Company") and a wholly owned subsidiary of Wave Life Sciences Ltd., a Singapore corporation (the "Parent Company"), and Kyle Moran ("Executive").

WHEREAS, Company wishes to employ Executive as its Chief Financial Officer;

WHEREAS, Executive represents that Executive possesses the necessary skills to perform the duties of this position and that Executive has no obligation to any other person or entity which would prevent, limit or interfere with Executive's ability to do so;

WHEREAS, Executive and Company desire to enter into an Employment Agreement, which, except as specifically set forth herein, supersedes and replaces the current employment arrangement dated as of July 2014, between Executive and Company (the "Prior Employment Agreement"), to assure the harmonious performance of the affairs of Company.

NOW, THEREFORE, in consideration of the mutual promises, terms, provisions, and conditions contained herein, the parties agree as follows:

1. Roles and Duties.

(a) Executive Role. Subject to the terms and conditions of this Agreement, Company shall employ Executive as its Chief Financial Officer reporting to Company's President and Chief Executive Officer. Executive accepts such employment upon the terms and conditions set forth herein, and agrees to perform to the best of Executive's ability the duties normally associated with such position and as determined by Company in its sole discretion. During Executive's employment, Executive shall devote all of Executive's business time and energies to the business and affairs of Company, provided that nothing contained in this Agreement shall prevent or limit Executive's right to manage Executive's personal investments on Executive's own personal time, including, without limitation the right to make passive investments in the securities of: (a) any entity which Executive does not control, directly or indirectly, and which does not compete with Company or the Parent Company, or (b) any publicly held entity so long as Executive's aggregate direct and indirect interest does not exceed two percent (2%) of the issued and outstanding securities of any class of securities of such publicly held entity. Nothing contained herein shall prevent any family member of Executive from contracting with, being employed by or obtaining an ownership interest in any entity, whether or not such entity competes with the Company or the Parent Company; provided, however, that such contract, employment, or ownership interest does not extend to or involve Executive. In addition, nothing in this Agreement shall require Executive to transfer, sell or otherwise divest himself of any investments Executive or Executive's family members hold as of the date hereof. During Executive's employment, Executive shall not engage in any other non-Company related business activities of any nature whatsoever (including board memberships) without the Company's prior written consent, which consent shall not be unreasonably withheld. In addition, and so long as such activities do not interfere with Executive's performance of Executive's duties hereunder (including Executive's full devotion of business time and energies to the business and affairs of Company, as described above), Executive also may participate in civic, charitable and professional activities, but shall not serve in any official capacity, including as a member of a board, without the prior written consent of the Company.

2. Term of Employment.

(a) Term. Subject to the terms hereof, Executive's employment hereunder shall commence as of the date hereof and shall continue until terminated hereunder by either party.

(b) Termination. Notwithstanding anything else contained in this Agreement, Executive's employment hereunder shall terminate upon the earliest to occur of the following:

(i) Death. Immediately upon Executive's death;

(ii) Termination by Company.

(A) If because of Executive's Disability (as defined below in Section 2(c)), written notice by Company to Executive that Executive's employment is being terminated as a result of Executive's Disability, which termination shall be effective on the date of such notice or such later date as specified in writing by Company;

(B) If for Cause (as defined below in Section 2(d)), written notice by Company to Executive that Executive's employment is being terminated for Cause, which termination shall be effective on the date of such notice or such later date as specified in writing by Company (subject to any applicable "cure" rights as provided in Section 2(d) below);

(C) If by Company for reasons other than under Sections 2(b)(ii)(A) or (B), written notice by Company to Executive that Executive's employment is being terminated, which termination shall be effective immediately after the date of such notice or such later date as specified in writing by Company.

(iii) Termination by Executive.

(A) If for Good Reason (as defined below in Section 2(e)), written notice by Executive to Company that Executive is terminating Executive's employment for Good Reason and that sets forth the factual basis supporting the alleged Good Reason, which termination shall be effective thirty (30) days after the date of such notice; provided that if Company has cured the circumstances giving rise to the Good Reason, then such termination shall not be effective; or

(B) If without Good Reason, written notice by Executive to Company that Executive is terminating Executive's employment, which termination shall be effective at least thirty (30) days after the date of such notice.

Notwithstanding anything in this Section 2(b), Company may at any point terminate Executive's employment for Cause prior to the effective date of any other termination contemplated hereunder.

(c) Definition of "Disability". For purposes of this Agreement, "Disability" shall mean Executive's incapacity or inability to perform Executive's duties and responsibilities as contemplated herein for one hundred twenty (120) days or more (cumulative or consecutive) within any rolling twelve (12) month period, because Executive's physical or mental health has become so impaired as to make it impossible or impractical for Executive to perform the duties and responsibilities contemplated hereunder. Determination of Executive's physical or mental health shall be determined by Company after consultation with a medical expert appointed by mutual agreement between Company and Executive who has examined Executive. Executive hereby consents to such examination and consultation regarding Executive's health and ability to perform as aforesaid.

(d) Definition of "Cause". As used herein, "Cause" shall include: (i) Executive's willful engagement in dishonesty, illegal conduct or gross misconduct, which is, in each case, materially injurious to the Company or any affiliate; (ii) Executive's significant insubordination; (iii) Executive's substantial malfeasance or nonfeasance of duty; (iv) Executive's repeated failure, inability or refusal to perform his duties hereunder in a manner that is materially injurious to the Company or any affiliate (other than by reason of Executive's Disability); (v) Executive's unauthorized disclosure of confidential information; (vi) Executive's embezzlement, misappropriation or fraud, whether or not related Executive's employment with the Company; or (vii) Executive's breach of a material provision of any employment, non-disclosure, invention assignment, non-competition, or similar agreement between Executive and Company; provided that "Cause" shall not be deemed to have occurred pursuant to subsections (ii), (iii) or (iv) hereof unless Executive has first received written notice specifying in reasonable detail the particulars of such grounds and that Company intends to terminate Executive's employment hereunder for such grounds, and if such grounds are reasonably capable of being cured within thirty (30) days, Executive has failed to cure such grounds within a period of thirty (30) days from the date of such notice (the "Cure Period"). During any such Cure Period, and in connection with Executive's ability to cure a for Cause termination as specifically set forth herein, Executive shall have an opportunity to make a presentation to the Company's Board of Directors in response to the asserted grounds for Cause termination. "Cause" is not limited to events which have occurred prior to the termination of Executive's service to Company, nor is it necessary that Company's finding of "Cause" occur prior to such termination. If Company determines, subsequent to Executive's termination of service but only after the notice, related process and Cure Period described above have been exhausted (if the applicable "Cause" sub-section is invoked), that either prior or subsequent to Executive's termination, Executive engaged in conduct which would constitute "Cause," then Executive shall be deemed to have been terminated for "Cause" and he shall have no right to any benefit or compensation under this Agreement, including, without limitation, any payments or benefits under Section 4(c) or Section 4(d) hereof (as applicable).

(e) Definition of "Good Reason". As used herein, a "Good Reason" shall mean the occurrence of any of the following events without Executive's written consent: (i) relocation of Executive's principal business location to a location more than fifty (50) miles from Executive's then-current business location; (ii) a material diminution in Executive's duties, authority or responsibilities; (iii) a material reduction in the Executive's Base Salary (other than as a result of a broad based reduction of salary similarly affecting other Company executives having comparable rank, authority and seniority); or (iv) any material breach of this Agreement by the Company; provided that (A) Executive provides Company with written notice that Executive intends to terminate Executive's employment hereunder for one of the grounds set forth in this Section 2(e) within thirty (30) days of such ground occurring, (B) if such ground is capable of being cured, the Company has failed to cure such ground within a period of thirty (30) days from the date of such written notice, and (C) Executive terminates Executive's employment within sixty-five days from the date that Good Reason first occurs. For purposes of clarification, the above-listed conditions shall apply separately to each occurrence of Good Reason and failure to adhere to such conditions in the event of Good Reason shall not disqualify Executive from asserting Good Reason for any subsequent occurrence of Good Reason. For purposes of this Agreement, "Good Reason" shall be interpreted in a manner, and limited to the extent necessary, so that it shall not cause adverse tax consequences for either party with respect to Section 409A ("Section 409A") of the Internal Revenue Code of 1986, as amended (the "Code") and any successor statute, regulation and guidance thereto.

3. Compensation.

(a) Base Salary. Company shall pay Executive a base salary (the "Base Salary") at the annual rate of $425,000. The Base Salary shall be payable in substantially equal periodic installments in accordance with Company's payroll practices as in effect from time to time. Company shall deduct from each such installment all amounts required to be deducted or withheld under applicable law or under any employee benefit plan in which Executive participates. The Base Salary will be reviewed annually and may be increased.

(b) Annual Performance Bonus. Executive shall be eligible to receive an annual cash bonus (the "Annual Performance Bonus"), with the target amount of such Annual Performance Bonus equal to forty-five percent (45%) of Executive's Base Salary in the year to which the Annual Performance Bonus relates, provided that the actual amount of the Annual Performance Bonus may be greater or less than such target amount. The Annual Performance Bonus shall be based on both corporate and individual performance objectives to be established by the Board of Directors of the Parent Company or an appropriate committee thereof by no later than March 1st of the applicable bonus year (the "Performance Objectives"). Whether and to what extent the Performance Objectives have been achieved and the amount of any Annual Performance Bonus payable hereunder shall be determined by the Board of Directors of the Parent Company (or an appropriate committee thereof) in its sole and absolute discretion. Executive must be employed by Company on the date on which the Annual Performance Bonus is paid in order to be eligible for, and to be deemed as having earned, such Annual Performance Bonus. The Company shall deduct from the Annual Performance Bonus all amounts required to be deducted or withheld under applicable law or under any employee benefit plan in which Executive participates.

(c) Equity. Executive may be eligible to receive equity awards under the applicable equity incentive plan of the Parent Company then in effect, as determined by the Board of Directors of the Parent Company or an appropriate committee thereof.

(d) Open Time Off. Executive is eligible to take paid time off for vacation and personal reasons in accordance with Company's Open Time Off policies as in effect from time to time. The guideline for such time off is 3-4 weeks per calendar year. This guideline excludes time off for illness, company-paid holidays, year-end shutdown and emergencies. Time off is to be scheduled to minimize disruption to Company's operations, pursuant to the terms and conditions of Company Open Time Off policy and practices as applied to senior executives of the Company. Time off is not earned or accrued, therefore there are no rollover of days from year to year, nor is payment made for unused time off upon separation from employment.

(e) Fringe Benefits. Executive shall be entitled to participate in all benefit/welfare plans, long-term incentive programs, and other fringe benefits provided to Company senior executives at comparable levels. The terms of any such programs and benefits will be governed by the applicable plan documents and Company policies in effect from time to time. Executive understands that, except when prohibited by applicable law, Company's benefit plans and fringe benefits may be changed, replaced, terminated, modified or amended by Company from time to time in its sole discretion.

(f) Reimbursement of Expenses. Company shall reimburse Executive for all ordinary and reasonable out-of-pocket business expenses incurred by Executive in furtherance of Company's business in accordance with Company's policies with respect thereto as in effect from time to time. Executive must submit any request for reimbursement no later than thirty (30) days following the date that such business expense is incurred. All reimbursements provided under this Agreement shall be made or provided in accordance with the requirements of Section 409A including, where applicable, the requirement that (i) any reimbursement is for expenses incurred during Executive's lifetime (or during a shorter period of time specified in this Agreement); (ii) the amount of expenses eligible for reimbursement during a calendar year may not affect the expenses eligible for reimbursement in any other calendar year; (iii) the reimbursement of an eligible expense shall be made no later than the last day of the calendar year following the year in which the expense is incurred; and (iv) the right to reimbursement or in kind benefits is not subject to liquidation or exchange for another benefit.

(g) Indemnification. Executive shall be entitled to indemnification with respect to Executive's services provided hereunder pursuant to applicable law, the terms and conditions of Company's organizational and governing documents, Company's directors and officers ("D&O") liability insurance policy, and Company's standard indemnification agreement for directors and officers as executed by Company and Executive.

4. Payments Upon Termination.

(a) Definition of Accrued Obligations. For purposes of this Agreement, "Accrued Obligations" means: (i) the portion of Executive's Base Salary that has accrued prior to any termination of Executive's employment with Company and has not yet been paid; and (ii) the amount of any expenses properly incurred by Executive on behalf of Company prior to any such termination and not yet reimbursed. Executive's entitlement to any other compensation or benefit under any plan of Company shall be governed by and determined in accordance with the terms of such plans, except as otherwise specified in this Agreement.

(b) Termination by Company for Cause, or by Executive Without Good Reason, or as a Result of Executive's Disability or Death. If Executive's employment hereunder is terminated by Company for Cause, by Executive without Good Reason, or as a result of Executive's Disability or Death, then Company shall pay the Accrued Obligations to Executive on or before the time required by applicable law following the effective date of such termination and shall have no further obligations to Executive.

(c) Termination by Company Without Cause or by Executive For Good Reason. In the event that Executive's employment is terminated by Company without Cause or Executive terminates Executive's employment for Good Reason, then, in addition to the Accrued Obligations, Executive shall receive the following, subject to the terms and conditions described in Section 4(e) (including Executive's execution of a release of claims):

(i) Severance Payments. Continuation of payments in an amount equal to (x) Executive's then-current Base Salary for a period of twelve (12) months, and (y) an amount equal to the target Annual Performance Bonus to which Executive may have been entitled for the year in which Executive's employment terminates, prorated to reflect that portion of the year in which Executive was employed, less all customary and required taxes and employment-related deductions, which amounts shall be paid over time in accordance with Company's normal payroll practices (provided such payments shall be made at least monthly), commencing on the first payroll date following the date on which the release of claims required by Section 4(e) becomes effective and non-revocable, but not after seventy (70) days following the effective date of termination from employment; provided, that if the 70th day falls in the calendar year following the year during which the termination or separation from service occurred, then the payments will commence in such subsequent calendar year; provided further that if such payments commence in such subsequent year, the first such payment shall be a lump sum in an amount equal to the payments that would have come due since Employee's separation from service.

(ii) Benefits Payments. Upon completion of appropriate forms and subject to applicable terms and conditions under the Consolidated Omnibus Budget Reconciliation Act of 1985, as amended ("COBRA"), the Company shall continue to pay its share of the costs for Employee's coverage under the Company's group health insurance plan, until the earlier to occur of twelve (12) months following Executive's termination date or the date Executive begins employment with another employer; provided that such Company-paid premiums may be recorded as additional income pursuant to Section 6041 of the Code and not entitled to any tax qualified treatment to the extent necessary to comply with or avoid the discriminatory treatment prohibited by the Patient Protection and Affordable Care Act of 2010 and the Health Care and Education Reconciliation Act of 2010 or Section 105(h) of the Code. Executive shall bear full responsibility for applying for COBRA continuation coverage and Company shall have no obligation to provide Executive such coverage if Executive fails to elect COBRA benefits in a timely fashion.

Payment of the above described severance payments and benefits are expressly conditioned on Executive's execution without revocation of the release of claims under Section 4(e) and return of Company property under Section 6. In the event that Executive is eligible for the severance payments and benefits under

this Section 4(c), Executive shall not be eligible for and shall not receive any of the severance payments and benefits as provided in Section 4(d).

(d) Termination by Company Without Cause or by Executive For Good Reason Following a Change of Control. In the event that a Change of Control (as defined below) occurs and within a period of one (1) year following the Change of Control, either Executive's employment is terminated by Company without Cause, or Executive terminates Executive's employment for Good Reason, then, in addition to the Accrued Obligations, Executive shall receive the following, subject to the terms and conditions described in Section 4(e) (including Executive's execution of a release of claims):

(i) Lump Sum Severance Payment. Payment of a lump sum amount equal to twelve (12) months of Executive's then-current Base Salary, less all customary and required taxes and employment-related deductions, paid on the first payroll date following the date on which the release of claims required by Section 4(e) becomes effective and non-revocable, but not after seventy (70) days following the effective date of termination from employment.

(ii) Separation Bonus. Payment of a separation bonus in an amount equal to the target Annual Performance Bonus to which Executive may have been entitled for the year in which Executive's employment terminates less all customary and required taxes and employment-related deductions, paid on the first payroll date following the date on which the release of claims required by Section 4(e) becomes effective and non-revocable, but not after seventy (70) days following the effective date of termination from employment.

(iii) Benefit Payments. Upon completion of appropriate forms and subject to applicable terms and conditions under the COBRA, the Company shall continue to pay its share of the costs for Employee's coverage under the Company's group health insurance plan, until the earlier to occur of twelve (12) months following Executive's termination date or the date Executive begins employment with another employer; provided that such Company-paid premiums may be recorded as additional income pursuant to Section 6041 of the Code and not entitled to any tax qualified treatment to the extent necessary to comply with or avoid the discriminatory treatment prohibited by the Patient Protection and Affordable Care Act of 2010 and the Health Care and Education Reconciliation Act of 2010 or Section 105(h) of the Code. Executive shall bear full responsibility for applying for COBRA continuation coverage and Company shall have no obligation to provide Executive such coverage if Executive fails to elect COBRA benefits in a timely fashion.

Payment of the above described severance payments and benefits are expressly conditioned on Executive's execution without revocation of the release of claims under Section 4(e) and return of Company property under Section 6. In the event that Executive is eligible for the severance payments and benefits under this Section 4(d), Executive shall not be eligible for and shall not receive any of the severance payments and benefits as provided in Section 4(c).

As used herein, a "Change of Control" shall mean (A) a merger or consolidation of the Parent Company whether or not approved by the Board of Directors, other than a merger or consolidation which would result in the voting securities of the Parent Company outstanding immediately prior thereto continuing to represent (either by remaining outstanding or by being converted into voting securities of the surviving entity or the parent of such corporation) more than 50% of the total voting power represented by the voting securities of the Parent Company or such surviving entity or parent of such corporation, as the case may be, outstanding immediately after such merger or consolidation; or (B) the sale or disposition by the Parent Company of all or substantially all of the Parent Company's assets in a transaction requiring shareholder approval; or (C) the transfer, sale or disposition by the Parent Company of 50% or more of its interest in Company.

(e) Execution of Release of Claims. Company shall not be obligated to pay Executive any of the severance payments or benefits described in this Section 4 unless and until Executive has executed (without revocation) a timely release of claims in a form acceptable to Company, which shall include a general release of claims against Company and Parent Company (including its and their affiliated entities, and its and their officers, directors, employees and others associated with such entities), a reaffirmation of Executive's covenants under the terms of the Agreement to Protect Confidential Information, Inventions and Business (as referenced in Section 5 below), as well as standard and reasonable terms regarding items such as mutual non-disparagement, confidentiality, cooperation and the like (the "Release Agreement"). The Release Agreement must be provided to Executive within fifteen (15) days following Executive's separation from service, and signed by Executive and returned to Company no later than sixty (60) days following Executive's separation from service (the "Review Period"). If Executive fails or refuses to return the Release Agreement within the Review Period, Executive's severance payments and benefits hereunder shall be forfeited.

(f) No Other Payments or Benefits Owing. The payments and benefits set forth in this Section 4 shall be the sole amounts owing to Executive upon termination of Executive's employment for the reasons set forth above and Executive shall not be eligible for any other payments or other forms of compensation or benefits. The payments and benefits set forth in Section 4 shall be the sole remedy, if any, available to Executive in the event that Executive brings any claim against Company relating to the termination of Executive's employment under this Agreement.

5. Prohibited Competition, Solicitation, and Non-Disclosure.

(a) Executive expressly acknowledges that: (i) there are competitive and proprietary aspects of the business of Company and its affiliates; (ii) during the course of Executive's employment, Company and/or its affiliates shall furnish, disclose or make available to Executive confidential and proprietary information and may provide Executive with unique and specialized training; (iii) such Confidential Information and training have been developed and shall be developed by Company and/or its affiliates through the expenditure of substantial time, effort and money, and could be used by Executive to compete with Company and/or its affiliates; and (iv) in the course of Executive's employment, Executive shall be introduced to customers and others with important relationships to Company and/or its affiliates, and any and all "goodwill" created through such introductions belongs exclusively to Company and its affiliates, including, but not limited to, any goodwill created as a result of direct or indirect contacts or relationships between Executive and any customers of Company and its affiliates. In light of the foregoing acknowledgements, Executive hereby (x) acknowledges that Executive previously executed and agrees to abide by the terms and conditions set forth in the Company's Agreement to Protect Confidential Information, Inventions and Business (attached hereto as Exhibit A) and the Company's Confidentiality and Information Systems Usage Agreement (attached hereto as Exhibit B), (y) reaffirms Executive's obligations under the terms of the previously executed Agreement to Protect Confidential Information, Inventions and Business and Confidentiality and Information Systems Usage Agreement, and (z) acknowledges and agrees that nothing herein shall impact or affect the continued validity of the previously executed Agreement to Protect Confidential Information, Inventions and Business and Confidentiality and Information Systems Usage Agreement.

(b) Executive hereby acknowledges and agrees that in consideration for Executive's non-competition covenant as set forth in Agreement to Protect Confidential Information, Inventions and Business, the Company is providing the Executive with eligibility to receive the certaion severance payments and benefits under the conditions set forth in Section 4 hereof. Executive further acknowledges and agrees that the aforementioned consideration is fair and reasonable consideration independent of the Executive's employment with the Company for purposes of Executive's non-competition covenant.

(c) Executive hereby expressly acknowledges and agrees that if Executive breaches any of the terms and/or conditions set forth in the Agreement to Protect Confidential Information, Inventions and Business

following a termination of Executive's employment either by Company without Cause or by Executive for Good Reason, then, in addition to the relief described in the Agreement to Protect Confidential Information, Inventions and Business, (i) Company shall cease providing the Executive with any further payments under Section 4(c) or 4(d) (as applicable) as of the date of such breach, (ii) Company shall not be obligated to provide Executive with, and Executive shall not be eligible or otherwise entitled to receive, any further payments or benefits from Company, (iii) Company's obligation to provide Executive with any further such payments or benefits shall be null and void, and of no further force or effect, and (iv) Company shall be entitled to recover, and Executive shall be obligated to repay to Company, any payments and the value of any benefits previously provided to Executive by Company under Section 4(c) or 4(d) (as applicable) prior to the date of Executive's breach of the Agreement to Protect Confidential Information, Inventions and Business.

6. Property and Records. Upon the termination of Executive's employment hereunder for any reason or for no reason, or if Company otherwise requests, Executive shall: (a) return to Company all tangible business information and copies thereof (regardless how such Confidential Information or copies are maintained), and (b) deliver to Company any property of Company which may be in Executive's possession, including, but not limited to, Blackberry-type devices, smart phones, laptops, cell phones, products, materials, memoranda, notes, records, reports or other documents or photocopies of the same.

7. Code Sections 409A and 280G.

(a) In the event that the payments or benefits set forth in Section 4 of this Agreement constitute "non-qualified deferred compensation" subject to Section 409A, then the following conditions apply to such payments or benefits:

(i) Any termination of Executive's employment triggering payment of benefits under Section 4 must constitute a "separation from service" under Section 409A(a)(2)(A)(i) of the Code and Treas. Reg. §1.409A-1(h) before distribution of such benefits can commence. To the extent that the termination of Executive's employment does not constitute a separation of service under Section 409A(a)(2)(A)(i) of the Code and Treas. Reg. §1.409A-1(h) (as the result of further services that are reasonably anticipated to be provided by Executive to Company at the time Executive's employment terminates), any such payments under Section 4 that constitute deferred compensation under Section 409A shall be delayed until after the date of a subsequent event constituting a separation of service under Section 409A(a)(2)(A)(i) of the Code and Treas. Reg. §1.409A-1(h). For purposes of clarification, this Section 7(a) shall not cause any forfeiture of benefits on Executive's part, but shall only act as a delay until such time as a "separation from service" occurs.

(ii) Notwithstanding any other provision with respect to the timing of payments under Section 4 if, at the time of Executive's termination, Executive is deemed to be a "specified employee" (within the meaning of Section 409A(a)(2)(B)(i) of the Code), then limited only to the extent necessary to comply with the requirements of Section 409A, any payments to which Executive may become entitled under Section 4 which are subject to Section 409A (and not otherwise exempt from its application) shall be withheld until the first (1st) business day of the seventh (7th) month following the termination of Executive's employment, at which time Executive shall be paid an aggregate amount equal to the accumulated, but unpaid, payments otherwise due to Executive under the terms of Section 4.

(b) It is intended that each installment of the payments and benefits provided under Section 4 of this Agreement shall be treated as a separate "payment" for purposes of Section 409A. Neither Company nor Executive shall have the right to accelerate or defer the delivery of any such payments or benefits except to the extent specifically permitted or required by Section 409A.

(c) Notwithstanding any other provision of this Agreement to the contrary, this Agreement shall be interpreted and at all times administered in a manner that avoids the inclusion of compensation in income under Section 409A, or the payment of increased taxes, excise taxes or other penalties under Section 409A. The parties intend this Agreement to be in compliance with Section 409A. Executive acknowledges and agrees that Company does not guarantee the tax treatment or tax consequences associated with any payment or benefit arising under this Agreement, including but not limited to consequences related to Section 409A.

(d) If any payment or benefit Executive would receive under this Agreement, when combined with any other payment or benefit Executive receives pursuant to a Change of Control (for purposes of this section, a "Payment") would: (i) constitute a "parachute payment" within the meaning of Section 280G the Code; and (ii) but for this sentence, be subject to the excise tax imposed by Section 4999 of the Code (the "Excise Tax"), then such Payment shall be either: (A) the full amount of such Payment; or (B) such lesser amount (with cash payments being reduced before stock option compensation) as would result in no portion of the Payment being subject to the Excise Tax, whichever of the foregoing amounts, taking into account the applicable federal, state and local employments taxes, income taxes, and the Excise Tax, results in Executive's receipt, on an after-tax basis, of the greater amount of the Payment notwithstanding that all or some portion of the Payment may be subject to the Excise Tax.

8. General.

(a) Notices. Except as otherwise specifically provided herein, any notice required or permitted by this Agreement shall be in writing and shall be delivered as follows with notice deemed given as indicated: (i) by personal delivery when delivered personally; (ii) by overnight courier upon written verification of receipt; (iii) by telecopy or facsimile transmission upon acknowledgment of receipt of electronic transmission; or (iv) by certified or registered mail, return receipt requested, upon verification of receipt.

Notices to Executive shall be sent to the last known address in Company's records or such other address as Executive may specify in writing.

Notices to Company shall be sent to:

Wave Life Sciences USA, Inc.
733 Concord Avenue
Cambridge, MA 02138
Tel: (617) 949-2900
Attn: Chief Executive Officer

With a copy to:

Wave Life Sciences USA, Inc.
733 Concord Avenue
Cambridge, MA 02138
Tel: (617) 949-2900
Attn: General Counsel

(b) Modifications and Amendments. The terms and provisions of this Agreement may be modified or amended only by written agreement executed by the parties hereto.

(c) Waivers and Consents. The terms and provisions of this Agreement may be waived, or consent for the departure therefrom granted, only by written document executed by the party entitled to the benefits of such terms or provisions. No such waiver or consent shall be deemed to be or shall constitute a waiver or consent with respect to any other terms or provisions of this Agreement, whether or not similar. Each such waiver or

consent shall be effective only in the specific instance and for the purpose for which it was given, and shall not constitute a continuing waiver or consent.

(d) Assignment. Company may assign its rights and obligations hereunder to any person or entity that succeeds to all or substantially all of Company's business or that aspect of Company's business in which Executive is principally involved. Executive may not assign Executive's rights and obligations under this Agreement without the prior written consent of Company.

(e) Governing Law/Dispute Resolution. This Agreement and the rights and obligations of the parties hereunder shall be construed in accordance with and governed by the law of the Commonwealth of Massachusetts, without giving effect to the conflict of law principles thereof. Any legal action or proceeding with respect to this Agreement shall be brought in the courts of the Commonwealth of Massachusetts or of the United States of America for the District of Massachusetts. By execution and delivery of this Agreement, each of the parties hereto accepts for itself and in respect of its property, generally and unconditionally, the non-exclusive jurisdiction of the aforesaid courts.

(f) Jury Waiver. ANY, ACTION, DEMAND, CLAIM, OR COUNTERCLAIM ARISING UNDER OR RELATING TO THIS AGREEMENT SHALL BE RESOLVED BY A JUDGE ALONE AND EACH OF COMPANY AND EXECUTIVE WAIVES ANY RIGHT TO A JURY TRIAL THEREOF.

(g) Headings and Captions. The headings and captions of the various subdivisions of this Agreement are for convenience of reference only and shall in no way modify or affect the meaning or construction of any of the terms or provisions hereof.

(h) Entire Agreement. This Agreement, together with the other agreements specifically referenced herein and the Exhibits attached hereto, embodies the entire agreement and understanding between the parties hereto with respect to the subject matter hereof and supersedes all prior oral or written agreements and understandings relating to the subject matter hereof, including, but not limited to, the Prior Employment Agreement. Notwithstanding the foregoing, nothing herein shall impact, affect, supersede, change, or modify the terms of the Agreement to Protect Confidential Information, Inventions and Business and/or the Confidentiality and Information Systems Usage Agreement that Exeutive previously executed with Company. No statement, representation, warranty, covenant or agreement of any kind not expressly set forth in this Agreement shall affect, or be used to interpret, change or restrict, the express terms and provisions of this Agreement.

(i) Counterparts. This Agreement may be executed in two or more counterparts, and by different parties hereto on separate counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument. For all purposes a signature by fax shall be treated as an original.

[Signature Page to Follow]

IN WITNESS WHEREOF, the parties hereto have executed this Agreement as of the date first written above.

KYLE MORAN

/s/ Kyle Moran
Signature
Address: [address]

WAVE LIFE SCIENCES USA, INC.

By: /s/ Linda Rockett
Name: Linda Rockett, Esq.
Title: SVP, General Counsel

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

The Board of Directors
Wave Life Sciences Ltd.:

We consent to the incorporation by reference in the registration statements (Nos. 333-243515, 333-243491 , 333-208598, 333-221480, 333-228308, 333-233054, and 333-234519) on Form S-8 and (Nos. 333-231382 and 333-233052) on Form S-3, as amended, of Wave Life Sciences Ltd. of our report dated March 4, 2021, with respect to the consolidated balance sheets of Wave Life Sciences Ltd. as of December 31, 2020 and 2019, the related consolidated statements of operations and comprehensive loss, Series A preferred shares and shareholders' equity, and cash flows for each of the years then ended, and the related notes, which report appears in the December 31, 2020 annual report on Form 10-K of Wave Life Sciences Ltd.

/s/ KPMG LLP

Boston, Massachusetts
March 4, 2021

Exhibit 31.1

CERTIFICATIONS UNDER SECTION 302

I, Paul B. Bolno, M.D., certify that:

1. I have reviewed this annual report on Form 10-K of Wave Life Sciences Ltd.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a) all significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 4, 2021

/s/ Paul B. Bolno, M.D.

Paul B. Bolno, M.D.
President and Chief Executive Officer
Principal Executive Officer

Exhibit 31.2

CERTIFICATIONS UNDER SECTION 302

I, Kyle Moran, certify that:

1. I have reviewed this annual report on Form 10-K of Wave Life Sciences Ltd.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   a) designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   b) designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   c) evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   d) disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   a) all significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   b) any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 4, 2021

/s/ Kyle Moran
Kyle Moran
Chief Financial Officer
Principal Financial Officer

Exhibit 32

CERTIFICATIONS UNDER SECTION 906

Pursuant to section 906 of the Sarbanes-Oxley Act of 2002 (subsections (a) and (b) of section 1350, chapter 63 of title 18, United States Code), each of the undersigned officers of Wave Life Sciences Ltd., a Singapore corporation (the "Company"), does hereby certify, to such officer's knowledge, that:

The Annual Report for the year ended December 31, 2020 (the "Form 10-K") of the Company fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, and the information contained in the Form 10-K fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: March 4, 2021

/s/ Paul B. Bolno, M.D.
Paul B. Bolno, M.D.
President and Chief Executive Officer
Principal Executive Officer

Dated: March 4, 2021

/s/ Kyle Moran
Kyle Moran
Chief Financial Officer
Principal Financial Officer