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, 2021

or

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

For the transition period from _____ to _____

Commission File Number: 001-40969

ENTRADA THERAPEUTICS, INC.
(Exact name of registrant as specified in its charter)

Delaware	**81-3983399**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification Number)**
6 Tide Street Boston, MA	**02210**
(Address of Principal Executive Offices)	**(Zip Code)**

Registrant's telephone number, including area code: (857) 520-9158

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

Title of Each Class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common Stock, par value $0.0001 per share	**TRDA**	**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 Section 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 registrant's common equity held by non-affiliates of registrant on November 5, 2021 was approximately $474.9 million based upon the closing sale price of the common stock as reported on The Nasdaq Global Market as of such date. The registrant has elected to use November 5, 2021, which was the final closing date of the Company's initial public offering, including the full exercise of the underwriters' option to purchase additional shares on the Nasdaq Global Market, as the calculation date because on June 30, 2021 (the last business day of the registrant's most recently completed second fiscal quarter) the registrant was a privately held company. In determining the market value of non-affiliate common stock, shares of the registrant's common stock beneficially owned by officers, directors and affiliates have been excluded. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

As of February 28, 2022, the registrant had 31,251,484 shares of common stock, $0.0001 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement for its 2022 Annual Meeting of Stockholders, which the registrant intends to file pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year ended December 31, 2021, are incorporated by reference into Part III of this Annual Report on Form 10-K.

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K (Annual Report) contains express or implied forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, 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 are based on our management's belief and assumptions and on information currently available to our management. These statements relate to future events or our future operational or financial performance, and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. Forward-looking statements contained in this Annual Report include, but are not limited to, statements about:

- the initiation, timing, progress, results and costs of conducting our research and development programs and our current and future preclinical studies and anticipated clinical trials, including statements regarding the timing of initiation and completion of studies or trials and related preparatory work, the period during which the results of the trials will become available, and our current and future programs;

- the ability of our preclinical studies and clinical trials to demonstrate safety and efficacy of our therapeutic candidates, and other positive results;

- the beneficial characteristics, and the potential safety, efficacy and therapeutic effects of our therapeutic candidates;

- the timing, scope and likelihood of regulatory filings and approvals, including timing of Investigational New Drug applications (INDs) and final U.S. Food and Drug Administration (FDA) approval of our current therapeutic candidates or any future therapeutic candidates;

- the timing, scope or likelihood of foreign regulatory filings and approvals;

- the ability to leverage our proprietary EEV Platform to efficiently develop additional therapeutic candidates, including by applying learnings from one program to other programs and from one indication to our other indications;

- our estimates of the number of patients that we will enroll and our ability to initiate, recruit and enroll patients in and conduct and successfully complete clinical trials at the pace that we project;

- the costs of manufacturing and our ability to scale-up our manufacturing and processing approaches to appropriately address our anticipated commercial needs, which will require significant resources;

- our ability to establish or maintain collaborations or strategic relationships and the ability and willingness of our third-party strategic collaborators to undertake research and development activities relating to our therapeutic candidates and discovery programs;

- our ability to obtain funding for our operations necessary to complete further development and commercialization of our therapeutic candidates;

- our ability to take advantage of expedited regulatory pathways for our therapeutic candidates;

- our ability to obtain and maintain regulatory approval of our therapeutic candidates;

- the implementation of our business model, and strategic plans for our business, therapeutic candidates, and technology;

- the scope of protection we are able to establish and maintain for intellectual property rights covering our therapeutic candidates and other therapeutic candidates we may develop, including the extensions of existing patent terms where available, the validity of intellectual property;

- rights held by third parties, and our ability not to infringe, misappropriate or otherwise violate any third-party intellectual property rights;
- the period over which we estimate our existing cash and cash equivalents will be sufficient to fund our future operating expenses and capital expenditure requirements;
- our financial performance and estimates of our future expenses, revenues, capital requirements, use of our cash reserves, and our needs for additional financing;
- future agreements with third parties in connection with the development and commercialization of our therapeutic candidates and any other approved product;
- the rate and degree of market acceptance and the size and growth potential of the markets for our therapeutic candidates, and our ability to serve those markets;
- our ability to contract with third-party suppliers and manufacturers and their ability to perform adequately;
- our ability to produce our therapeutic candidates with advantages in turnaround times or manufacturing cost;
- our competitive position and the success of competing therapies that are or may become available;
- our need for and ability to attract and retain key scientific, management and other personnel and to identify, hire and retain additional qualified professionals;
- our expectations regarding the period during which we will remain an emerging growth company under the Jumpstart Our Business Startups Act of 2012 (the JOBS Act);
- our anticipated use of our existing resources;
- the effect of the ongoing coronavirus, or COVID-19, pandemic, including mitigation efforts and economic effects, on any of the foregoing or other aspects of our business operations, including but not limited to our preclinical studies and future clinical trials; and
- other risks and uncertainties, including those listed under the caption “Risk Factors.”

In some cases, you can identify forward-looking statements by terminology such as “may,” “might,” “will,” “could,” “would,” “should,” “expect,” “plan,” “anticipate,” “intend,” “believe,” “expect,” “estimate,” “seek,” “predict,” “future,” “project,” “potential,” “continue,” “target” or the negative of these terms or other comparable terminology, and similar expressions, although not all forward-looking statements contain these identifying words. These statements are only predictions. You should not place undue reliance on forward-looking statements because they involve known and unknown risks, uncertainties, and other factors, which are, in some cases, beyond our control and which could materially affect results. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed under the section titled “Risk Factors” and elsewhere in this Annual Report. If one or more of these risks or uncertainties occur, or if our underlying assumptions prove to be incorrect, actual events or results may vary significantly from those implied or projected by the forward-looking statements. No forward-looking statement is a guarantee of future performance. You should read this Annual Report and the documents that we reference in this Annual Report and have filed with the Securities and Exchange Commission (the SEC) thereto completely and with the understanding that our actual future results may be materially different from any future results expressed or implied by these forward-looking statements.

You should read this Annual Report on Form 10-K and the documents that we reference herein and have filed or incorporated by reference as exhibits hereto completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

This Annual Report also contains estimates, projections and other information concerning our industry, our business and the markets for our product candidates. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances that are assumed in this information. Unless otherwise expressly stated, we obtained this industry, business, market, and other data from our own internal estimates and research as well as from reports, research surveys, studies, and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data and similar sources. All of the market data used in this Annual Report involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data. Industry publications and third-party research, surveys, and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. Our estimates of the potential market opportunities for our product candidates include several key assumptions based on our industry knowledge, industry publications, third-party research, and other surveys, which may be based on a small sample size and may fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions.

SUMMARY OF MATERIAL AND OTHER RISKS ASSOCIATED WITH OUR BUSINESS

Our business is subject to numerous risks and uncertainties and are subject to change based on various factors, including those highlighted in the section entitled "Risk Factors" and elsewhere in this Annual Report on Form 10-K (Annual Report). These risks include, but are not limited to, the following:

- We have a limited operating history, have incurred significant operating losses since our inception and expect to incur significant losses for the foreseeable future. We may never generate any revenue or become profitable or, if we achieve profitability, we may not be able to sustain it.

- We will require additional financing to achieve our goals, and a failure to obtain this necessary capital when needed on acceptable terms, or at all, could force us to delay, limit, reduce or terminate our development programs, commercialization efforts or other operations.

- We are early in our development efforts. We have not initiated clinical studies, and as a result it will be years before we commercialize a therapeutic candidate, if ever. If we are unable to identify and advance therapeutic candidates through preclinical studies and clinical trials, obtain marketing approval and ultimately commercialize them, or experience significant delays in doing so, our business will be materially harmed.

- Our business is highly dependent on the clinical advancement of our programs and modalities and is especially dependent on the success of our lead EEV therapeutic candidate, ENTR-601-44. Delay or failure to advance programs or modalities, including ENTR-601-44 could adversely impact our business.

- Our EEV therapeutic candidates are based on a novel therapeutic approach, which makes it difficult to predict the time and cost of development and of subsequently obtaining regulatory approval, if at all.

- Preclinical and clinical development involves a lengthy and expensive process with an uncertain outcome, and the results of preclinical studies are not necessarily predictive of the results of later preclinical studies and any clinical trials of our therapeutic candidates. We have not tested any of our therapeutic candidates in clinical trials and our therapeutic candidates may not have favorable results in clinical trials, if any, or receive regulatory approval on a timely basis, if at all.

- Substantial delays in the commencement, enrollment or completion of our planned clinical trials or failure to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities could prevent us from commercializing any therapeutic candidates we determine to develop on a timely basis, if at all.

- Our approach to the discovery and development of therapeutic candidates based on our EEV Platform is unproven, and we do not know whether we will be able to develop any products of commercial value, or if competing technological approaches will limit the commercial value of our therapeutic candidates or render our EEV Platform obsolete.

- We rely, and expect to continue to rely, on third parties to conduct some or all aspects of our product manufacturing, research and preclinical and clinical testing, and these third parties may not perform satisfactorily or, dedicate adequate resources to meet our needs, or may be unable to acquire the necessary supplies to perform successfully.

- We face significant competition, and if our competitors develop technologies or therapeutic candidates more rapidly than we do or their technologies are more effective, our business and our ability to develop and successfully commercialize products may be adversely affected.

- We expect to expand our development and regulatory capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

- While we will attempt to diversify our risks by developing one or more programs in each modality, there are risks that are unique to each modality and risks that are applicable across modalities. These risks may impair our ability to advance one or more of our programs in clinical development, obtain regulatory approval, or ultimately commercialize our programs, or cause us to experience significant delays in doing so, any of which may materially harm our business.

- If we are unable to obtain and maintain patent protection for our EEV Platform, therapeutic development programs and other proprietary technologies we develop, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize products and technology similar or identical to ours, and our ability to successfully commercialize our therapeutic programs and other proprietary technologies we may develop may be adversely affected.

- Our future success depends on our ability to retain key employees and to attract, retain and motivate qualified personnel.

- Unstable market and economic conditions may have adverse consequences for our business, financial condition and stock price.

The material and other risks summarized above should be read together with the text of the full risk factors and in the other information set forth in this Annual Report, including our consolidated financial statements and the related notes, as well as in other documents that we file with the Securities and Exchange Commission (the SEC). If any such material and other risks and uncertainties actually occur, our business, prospects, financial condition and results of operations could be materially and adversely affected. The risks summarized above or described in full are not the only risks that we face. Additional risks and uncertainties not currently known to us, or that we currently deem to be immaterial may also materially adversely affect our business, prospects, financial condition and results of operations.

PART I

Item 1. Business

Overview

We aim to transform the lives of patients by establishing Endosomal Escape Vehicle (EEV) therapeutics as a new class of medicines and we aim to become the world's foremost intracellular therapeutics company. EEV therapeutics are comprised of small cyclic peptides that are chemically conjugated to a wide range of specific and active biological therapeutics. Our EEV therapeutics are designed to engage intracellular targets that have long been considered inaccessible and undruggable. Through our proprietary, highly versatile and modular EEV platform (EEV Platform), we are building a robust development portfolio of EEV therapeutic candidates designed to enable the efficient intracellular delivery of therapeutics in various organs and tissues with an improved therapeutic index. We believe that the potential success of our early programs can translate into the efficient development of additional EEV therapeutic candidates and allow us to build portfolios in rare disease, immunology and oncology.

We are initially focused on the development of EEV therapeutics for rare neuromuscular diseases, including Duchenne muscular dystrophy (DMD) and myotonic dystrophy type 1 (DM1). DMD is caused by genetic mutations that prevent the creation of functional dystrophin, a protein required to maintain the structural integrity of muscle cells. In our neuromuscular disease programs, we link EEVs to small strands of nucleic acids called oligonucleotides, including phosphorodiamidate morpholino oligomers (PMOs). We are developing EEV-PMOs that promote the skipping of these mutations associated with DMD. We believe that our EEV-PMO exon-skipping therapy will enable the production of functional dystrophin to slow, stop or even reverse disease progression. Our most advanced therapeutic candidate, ENTR-601-44, is being developed for patients with DMD that are exon 44 skipping amenable. We plan to submit an Investigational New Drug (IND) application to the U.S. Food and Drug Administration (FDA) for ENTR-601-44 in 2022. We are developing a second lead program, EEV-PMO-CAG, for patients with DM1. Patients with DM1 carry extra cytosine-uracil-guanine (CUG) triplet repeats that result in misprocessing of several proteins and multisystemic clinical manifestations. Our EEV-PMO-CAG for DM1 is designed to block the triplet repeats in the messenger RNA (mRNA) that sequesters these critical proteins and restore muscle function. We plan to submit an IND to the FDA for EEV-PMO-CAG, for the treatment of DM1, in 2023.

Approximately 75% of all disease-causing targets are located inside cells. Intracellular therapeutics are designed to correct disease-causing dysfunction inside cells, addressing targets at the level of DNA, RNA or protein. In order to do so, these therapeutics need to first get through the cell's membrane, which is a phospholipid bilayer, and then escape from the cell's transportation and sorting vehicle, known as the early endosome, in order to reach and engage with their intended targets. Small molecules can permeate cell membranes but tend to be rapidly cleared by the body before they reach the intended tissue and can be associated with off-target effects. These limitations often necessitate high therapeutic doses and can be associated with less-than-optimal therapeutic activity. Biological therapeutics are generally potent and specific with respect to their intracellular targets of interest but limited in their ability to reach such targets, often lacking the ability to efficiently penetrate the cell membrane and then escape from the early endosome.

We believe our EEV Platform can enable the efficient intracellular delivery of specific and potent therapeutics. The following key attributes of our EEV Platform have allowed us to develop broadly distributed, EEV therapeutic candidates, which have been observed to be pharmacologically or biologically active and targeted with respect to the engagement or involvement with a desired intracellular target of interest.

- ***Serum stability and extended half-life:*** Based on preclinical studies, we have observed that EEVs have increased stability and extended half-life due to their unique cyclic structure, which limits protease-mediated degradation. We believe this may enable increased systemic exposure.

- ***Broad biodistribution:*** EEVs target phospholipid bilayers, which we believe can enable delivery to any cell in the body, regardless of route of administration. We have shown biodistribution to a wide range of organs, tissues and cells in our preclinical studies, including cardiac muscle, the cerebellum and macrophages, among many others.

- ***Active uptake and drug release:*** EEVs generally avoid being trapped in the cell membrane and are instead taken up into the cell by the early endosome. EEVs then enable budding of vesicles from the early endosome, which we believe substantially increase the level of therapeutics reaching intended targets within the cell.

We believe our EEV Platform can offer meaningful advantages over existing therapeutic approaches, including:

- ***Broad potential therapeutic index*** based on observations in preclinical studies. We believe EEV therapeutic candidates can engage targets across various organs and tissues with up to 50 times greater intracellular target exposure compared with a similar dose regimen of an unconjugated therapeutic.

- ***Potential utility across multiple modalities*** due to the ability of EEVs to facilitate intracellular uptake of proprietary therapeutic candidates ranging in size from 1 kDa to 600 kDa, including oligonucleotides, peptides, antibodies and larger multimeric proteins.

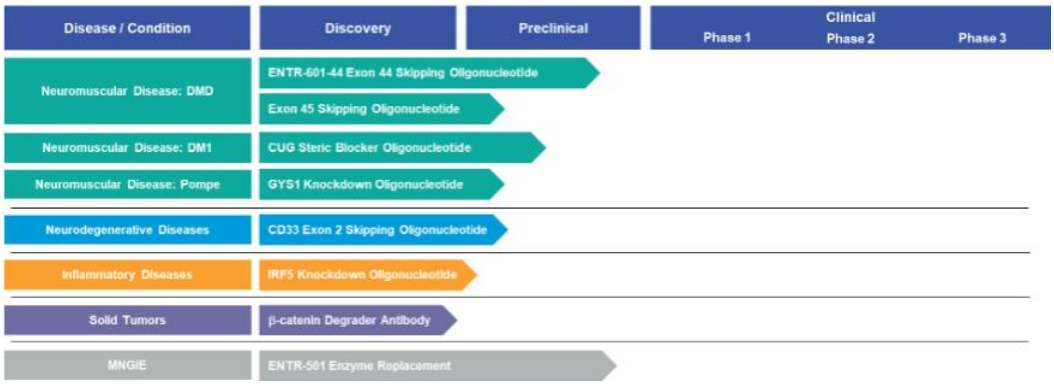
- ***Potential applicability to a wide range of diseases*** as we believe EEVs can enter cells by binding with the phospholipid bilayer which is common to all cells, tissues and organs in the body. This may imply an ability to achieve both systemic and specific delivery of potential therapeutic candidates for a wide range of diseases.

- ***Multiple delivery routes*** possible including intravenous (IV), intramuscular (IM), subcutaneous (SQ) and intrathecal (IT) injections to deliver our EEV therapeutic candidates and generate functional outcomes.

- ***Modular approach supports efficient expansion of development into multiple therapeutic areas,*** including oligonucleotide therapies in rare disease and immunology, antibody-based protein degraders in oncology and enzyme replacement therapy in rare disease.

- ***A simple and scalable construct designed to translate from preclinical to clinical development*** as EEVs have been manufactured efficiently to clinical scale and the small size of EEVs may limit the risk of immunogenicity. In addition, acute and chronic toxicology studies in the ENTR-501 program have demonstrated the potential to deliver clinically-relevant doses in a non-human primate (NHP) with favorable tolerability.

Through our EEV Platform, we aim to create a diverse and expanding development portfolio of oligonucleotide, antibody and enzyme-based programs as summarized in the graphic below.



Neuromuscular Diseases

In neuromuscular disease, we are initially focused on the development of disease-modifying treatments for DMD. DMD is a monogenic X-linked disease caused by mutations in the DMD gene, which encodes for the protein dystrophin. We estimate that DMD occurs in approximately one in every 3,500 to 5,000 live male births and that the

patient population is approximately 30,000 patients in the aggregate in the United States and Europe. Approximately 80% of patients have mutations amenable to exon skipping in the nucleus. We are developing therapeutic candidates to address the genetic basis, at the exon-specific level, of DMD. EEV oligonucleotides are designed to promote the skipping of exon mutations associated with DMD, enabling muscle cells to create a functional dystrophin at a level that we believe may slow, stop or even reverse DMD progression. We are initially focusing on the development of an EEV-PMO, ENTR-601-44, for patients with DMD that are exon 44 skipping amenable, who represent approximately 7.6% of the total DMD population with significant unmet medical need. We have observed substantial exon skipping (50%-100%) and dystrophin production of up to approximately 70% of wild-type levels in mice, which is durable at eight weeks. Our preclinical studies have also demonstrated reductions in serum creatine kinase (CK), which is a commonly-used biomarker of muscle breakdown, to wild-type levels. Correction of CK is believed to be a strong indicator of pharmacodynamic activity throughout the body and has been described in medical literature as a marker of muscle integrity. We have observed corresponding and significant improvements in functional outcomes as measured in the D2-mdx mouse. In particular, we have observed meaningful tissue uptake and exon skipping, ranging from approximately 60% to over 95% depending on the tissue, in the D2-mdx mouse. In this model, in EEV-PMO treated tissues we observed substantial restoration of both dystrophin and alpha sarcoglycan. In striated muscle, sarcoglycans interact with dystrophin and other dystrophin-associated proteins to form the dystrophin-associated glycoprotein complex which protects the sarcolemma from contraction-induced injury. Finally, we have observed extended PK and high levels (almost 90% in the biceps) of exon skipping in a NHP with ENTR-601-44. We are also developing an EEV-PMO for patients with exon 45 skipping amenable mutations, which population represents approximately 8% of the total DMD population. We plan to submit an IND to the FDA for ENTR-601-44 in 2022 and to select an exon 45 skipping candidate in 2022.

We are developing a second lead program for patients with DM1. DM1 is a rare disease caused by a mutation driven alteration of normal RNA structure manifesting as an increase in the number of CTG triplet repeats found in the 3' non-coding region of the DM1 protein kinase (DMPK) gene. The resulting transcripts, which contain an expanded CUG tract, aggregate in discrete foci in the nuclei of DM patient cells. The excessive number of CUG repeats impart toxic activity, referred to as a toxic gain-of-function. Multiple key proteins are misprocessed, and this contributes to the multisystemic nature of the disease, which includes generalized limb weakness, respiratory muscle impairment, cardiac abnormalities, fatigue, gastrointestinal complications, cataracts, incontinence and excessive daytime sleepiness. DM1 is commonly estimated to affect over 40,000 people in the United States and over 50,000 in Europe. Our approach is intended to address the underlying cause of the disease by targeting the extra CUG triplet repeats responsible for the downstream misprocessing of proteins important to cell growth, metabolism and function. EEV-PMO-CAG is designed to block the triplet repeats and correct the mis-splicing and aberrant expression of downstream transcripts in order to restore tissue function. Our preclinical studies have resulted in *in vitro* and *in vivo* data where we have observed splicing correction across multiple transcripts, durable DMPK mRNA knockdown, reduction of foci, rapid phenotypic correction, and tolerability in murine models of DM1 which exhibit expanded CTG and CUG repeats. We expect to announce a candidate for the potential treatment of DM1 and additional supporting data in early 2022, and expect to submit an IND for such therapeutic candidate to the FDA in 2023.

We believe our EEV Platform has broad applicability across multiple neuromuscular diseases. In addition to DMD and DM1, we are leveraging this platform to explore EEV oligonucleotides for the potential treatment of Pompe disease. Pompe disease is a rare, autosomal recessive lysosomal storage disease caused by a mutation in the gene that encodes for glucosidase alpha acid (GAA), which results in an absence or deficiency of GAA protein that is essential to the breakdown of complex sugar, glycogen. Excess glycogen in the muscle cell leads to tissue damage and loss of function. Pompe disease is commonly estimated to affect between 5,000 and 10,000 patients in the aggregate in the United States and Europe; however, the advent of newborn screening suggests the disease is underdiagnosed. Our Pompe disease program focuses on the development of a potentially disease-modifying treatment by utilizing an EEV therapeutic candidate that targets and degrades the mRNA-encoding glycogen synthetase 1 (GYS1), a protein required for the synthesis of glycogen which powers in muscle cells. Our preclinical data has shown superior and dose-dependent EEV-PMO knockdown of GYS1 gene expression (approximately 95%) and protein production in skeletal and cardiac muscles versus PMO alone. Further, protein level reductions were durable to eight weeks post IV dose of 13.5 mg/kg EEV-PMO.

Immunology

In immunology, we are currently leveraging multiple oligonucleotide strategies to downregulate the expression of Interferon Regulatory Factor 5 (IRF5). IRF5 activation is a master switch implicated in the inflammatory and fibrotic

processes associated with non-alcoholic steatohepatitis, systemic lupus erythematosus, inflammatory bowel disease, rheumatoid arthritis, type 2 diabetes, asthma and neuropathic pain, among many others. We have observed knockdown of the problematic IRF5 protein both *in vitro* and *in vivo*. We are currently optimizing the EEV-PMO constructs and conducting experiments evaluating the delivery of IRF5-targeting EEV-PMOs in disease models. Results from these experiments, including potential proof-in-concept are expected in 2022. Pending positive results, we plan to select our first immunology therapeutic candidate by the end of 2023.

Oncology

In oncology, we believe our EEV Platform has the potential to deliver highly selective large molecule protein degraders against disease-causing proteins. We are actively working towards an oncology therapeutic candidate selection for biologically validated targets that have been undruggable or have been sub-optimally drugged. We are initially focused on β-catenin, a protein which contributes to the carcinogenesis, tumor progression and metastasis of several cancers, including colon, liver, pancreatic, lung, breast and ovarian cancer. We have observed that EEV conjugation to a receptor-targeted antibody enhances meaningful modulation of intracellular signaling.

Metabolic Disease

Our ENTR-501, an intracellular thymidine phosphorylase (TP) enzyme replacement therapy (ERT), program is in development for the treatment of mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). MNGIE is a slowly progressive, rare disease characterized by elevated levels of thymidine. Preliminary preclinical studies have demonstrated that ENTR-501 reduces toxic thymidine levels below those observed in wild-type mice. We have completed IND-enabling studies for the MNGIE program, including pharmacodynamic and pharmacokinetic studies in mice, and pharmacokinetic and chronic toxicology in NHPs. In 2020, we made the strategic decision to focus the majority of our immediate efforts on EEV-oligonucleotide opportunities. In order to support ENTR-501 progress, we are exploring partnership opportunities with organizations that have the resources and expertise to continue the development of ENTR-501 into and through clinical development. We continue to believe that the program will have an important role in the future treatment of patients with MNGIE.

Additional Discovery Programs

We are leveraging the modularity of our EEV Platform to develop opportunities as diverse as EEV-CRISPR-Cas delivery for gene editing, EEV-antibody drug conjugates, EEV-oligonucleotide opportunities for central nervous system (CNS) and peripheral nervous system (PNS) disorders, EEV-antibody oligonucleotide conjugates for enhanced tissue tropism and blood brain barrier carriage, as well as novel EEV-ERT therapies. We regularly explore strategic opportunities to develop therapies where we believe our EEV Platform will make a difference for patients with devastating diseases.

Our Strategy

We aim to transform the lives of patients by establishing EEV therapeutics as a new class of medicines and we aim to become the world's foremost intracellular therapeutics company. To achieve this, the key pillars of our strategy include:

- **Rapidly advance EEV-PMO therapeutic candidates into clinical development in patients with DMD and DM1.** Our DMD portfolio is comprised of exon-skipping EEV-PMO therapies that aim to restore functional dystrophin production. We have initially prioritized our DMD development efforts on exon 44 and 45 skipping amenable mutations, due to the profound unmet need in these respective patient populations. We plan to advance our most advanced lead EEV-PMO therapeutic candidate, ENTR-601-44, which targets the skipping of exon 44, to Investigational New Drug (IND) filing with the FDA in 2022. Following proof-of-concept of ENTR-601-44 we plan to expand our DMD franchise by discovering and developing therapeutic candidates for additional patient subpopulations. We are developing a second program for patients with DM1 and plan to submit an IND to the FDA for an EEV-PMO-CAG candidate in 2023. We believe that we can leverage our EEV, linker and oligonucleotide optimization process and build upon the potential success of each exon skipping therapeutic candidate. For example, we believe that potential technical success in DM1, which involves correcting for a toxic gain of function, could be broadly applicable within and beyond neuromuscular diseases.

- **Leverage the modularity of our platform to advance a broad development portfolio of EEV therapeutic candidates across multiple devastating diseases**. We believe our modular EEV Platform can enable us to advance therapeutic candidates for the treatment of additional neuromuscular diseases for which the biophysical properties, therapeutic approaches, and development strategies are similar to DMD which involves upregulating gene and protein expression and DM1 which involves downregulating protein expression through the normalization of alternate splicing. Initially we intend to broaden our disease portfolio into Pompe disease, while assessing the potential to use the same therapeutic candidate in multiple glycogen storage disorders. We plan to advance additional programs outside of neuromuscular diseases leveraging a variety of EEV-PMO strategies to downregulate gene expression with a focus on broadly applicable intracellular targets central to a variety of indications beyond neuromuscular disease.

- **Continue to invest in and build upon our EEV Platform to extend our pioneering position in developing novel EEV-based therapeutic candidates.** We plan to continue to invest in our platform and expand our library of EEVs by optimizing the EEV chemistry for specific modalities, including oligonucleotide, antibody and enzyme-based therapeutic candidates. We are also leveraging the modularity of the platform to combine different elements such as antibody-guided oligonucleotide constructs to enhance tissue tropism and enzyme and guide RNA associations to enable gene editing. We further plan to explore the flexibility of the platform and pursue alternative therapeutic approaches to the same fundamental challenges; for example, to use EEV antibodies to degrade a pathogenic protein or to use EEV- PMO approaches to prevent the production of that same protein.

- **Selectively evaluate strategic partnerships to maximize the therapeutic potential of our EEV Platform**. We aim to improve patients' lives and plan to utilize our library of EEVs to enable strategic partnerships with the goal of expanding our therapeutic footprint, and to accelerate the development of certain programs.

Our Team and Culture

Our patient-focused culture drives our shared mission of developing intracellular therapeutics for patients with devastating diseases. We are committed to building and maintaining a deep connection with the patients, caregivers, research community and physicians that we serve.

Our management team brings a depth of experience and knowledge base in platform research, drug discovery and development and commercialization. The team is led by Dipal Doshi, our President and Chief Executive Officer, who brings over 20 years of leadership experience within life sciences companies; Natarajan Sethuraman, Ph.D., our Chief Scientific Officer, who is an expert in large molecule therapeutic development and delivery platforms with over 30 years of experience across pharmaceutical and biotechnology companies; Nerissa Kreher, M.D., our Chief Medical Officer, a physician executive with a 15-year record of driving growth at start-ups and larger biotech/pharma companies and with extensive experience in rare disease research; Nathan Dowden, our Chief Operating Officer, who has almost three decades of experience leading corporate strategy, portfolio management, business planning and operations; Kory Wentworth, our Chief Financial Officer, who has 20 years of public accounting and global biopharmaceutical experience and our General Counsel, Jared Cohen Ph.D., J.D., who has 20 years of both external and in-house experience at a range of mature and early stage biopharmaceutical companies. Our leadership team also includes, Karla MacDonald, our Vice President of Corporate Communications, and Kerry Robert, M.S., our Vice President of People. As of December 31, 2021, our organization was comprised of 102 talented individuals with significant experience across discovery, preclinical research, manufacturing, clinical development and operations. We are supported by leading scientific and clinical experts in the fields of peptide chemistry, oligonucleotide and protein optimization, disease specific pathophysiology and clinical development.

Since our inception, we have raised over $400 million in private and public capital from leading biotechnology investors.

Our Platform

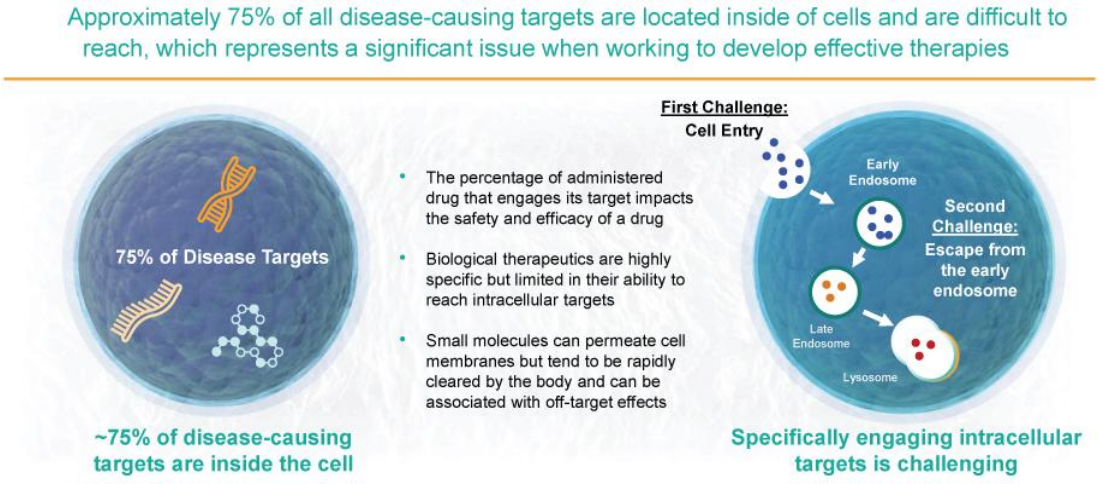
Biology of Intracellular Trafficking

Each person's genetic material, or genome, consists of DNA in sequences of genetic code called genes. Many diseases, including rare genetic diseases, immune-mediated disorders and cancers, are caused by a mutation in an individual's DNA sequence, as compared to a healthy individual. These mutations can be in a single gene, and result in monogenic disorders, or in multiple genes. This genetic dysregulation can be inherited or can be caused by damage to the DNA. In each case, a mutation results in a change in the information that DNA provides to the cell's protein manufacturing and processing functions, which in turn result in either a lack of useful protein, an excess of toxic protein, or a dysregulation of cell signaling mechanisms. These changes manifest in pathological dysfunction at the cellular, tissue, organ and potentially systemic level.

As pathological dysfunction occurs inside the cell, intracellular therapeutics are designed to correct disease-causing dysfunction at either the level of DNA, RNA, or protein. Therapeutic modalities which prevent or enhance protein production include small molecules, viral gene therapies and oligonucleotide therapeutics, including anti-sense oligonucleotides (ASOs) and small interfering RNAs (siRNAs). Therapeutic modalities which target aberrant proteins include small molecules, enzymes, antibodies and peptides.

Despite significant advances in understanding disease drivers, obstacles to effective treatment remain, in part because approximately 75% of all disease-causing targets are located inside of cells. Small molecules can permeate cell membranes but tend to be rapidly cleared by the body before they reach the intended tissue and can be associated with off-target effects. These limitations often necessitate high therapeutic doses and can be associated with less-than-optimal therapeutic activity.

On the other hand, biological therapeutics are highly targeted and potent but are limited in their ability to reach intracellular targets of interest. The first challenge is to get biological therapeutics, such as proteins and nucleic acids, through the phospholipid bilayer. Proteins and nucleic acids can be internalized through endocytosis, a natural process by which substances are brought into the cell. Once endocytosis begins, the cell membrane folds around the biological therapeutic and internalizes it, fusing with it and trapping it in a structure called the early endosome. The early endosome serves as a sorting vehicle, either returning its contents back to the cell membrane or transporting and slowly degrading them in the late endosome and, ultimately, in the lysosome.



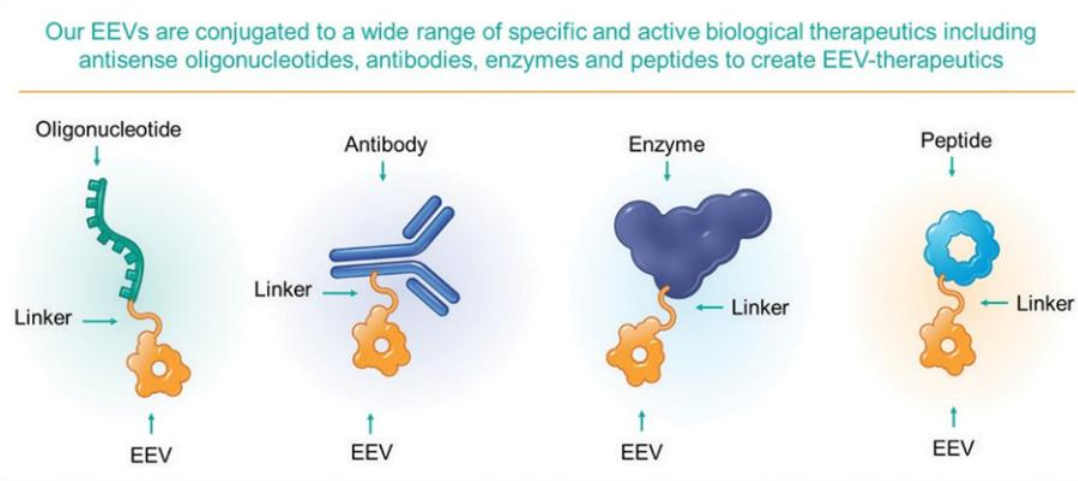
The second challenge is achieving endosomal escape, wherein the biological therapeutic is released in functional form from the early endosome. Even when a therapeutic is successful in penetrating a cell, only about 1% of the drug will escape the early endosome to reach its intended intracellular targets. As a result, high doses of drug product are often needed to produce a therapeutic effect, which could potentially cause systemic dose-related toxicity. While scientific advances using lipid particles, viral vectors, antibodies and prior generations of cell-penetrating peptides to

deliver biological therapeutics have been made, these vehicles are often relatively toxic, limited in their applicability and/or difficult to manufacture.

To effectively capitalize on both known biology and future discoveries, a better way of targeted intracellular delivery of therapeutics is needed. We believe we have discovered a potential solution.

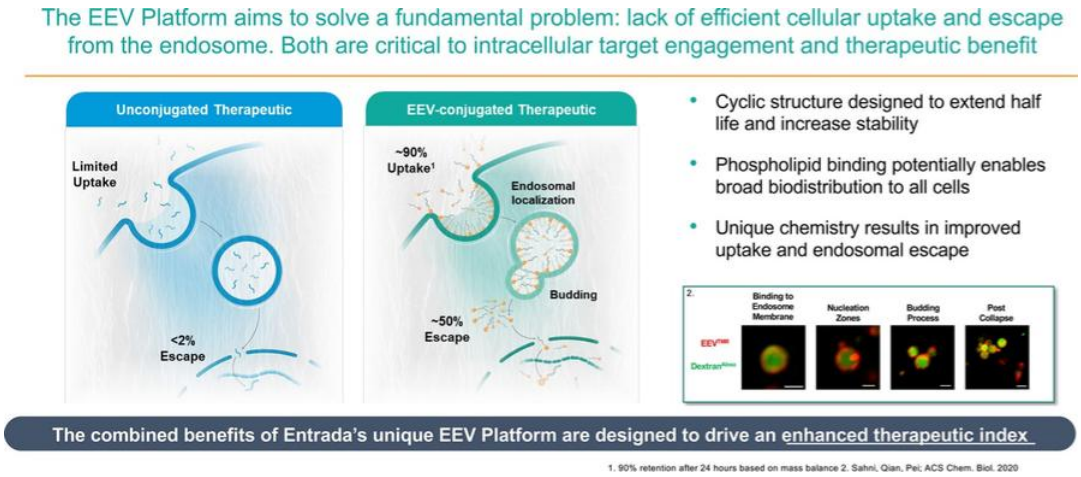
Our Approach

An ideal therapeutic platform enables the efficient intracellular delivery of highly targeted and potent therapeutics throughout the body. The cornerstone of our platform, our proprietary EEVs are comprised of small cyclic peptides of approximately 10 amino acid residues or fewer. EEVs bind with low affinity, at normal serum pH levels, directly to the phospholipid bilayer of all cells and trigger the natural process of endocytosis. EEVs are chemically conjugated to a wide range of specific and potent biological therapeutics, including, for example, small snippets of therapeutic RNA (ASOs), antibodies and large enzymes, to create EEV therapeutic candidates.



Once the EEV-conjugated material binds to the phospholipid bilayer, the cell engulfs the conjugate and brings it inside. EEVs are designed to enable cellular uptake into every type of tissue in the body. In addition to the potential for broad cellular distribution, we believe EEVs can also, if needed, be tailored to specific cell types or tissues through the conjugation of high affinity cell-receptor antibodies, wherein the picomolar to nanomolar level receptor binding affinity would be expected to easily out-compete the low affinity phospholipid binding activity of the EEV.

In our preclinical studies, we have observed, based on mass balance analysis, that greater than 90% of EEV-conjugated material is taken up by the tissues of the body. Once inside the cell, these studies indicate that the EEV-conjugated material rapidly escapes from the early endosome. Because of the low-pH conditions in the early endosome, the binding affinity of the EEV to the inner endosome wall increases, resulting in the successful formation and budding of unstable vesicles which then collapse and release their contents into the cell cytosol. In our preclinical studies, we observed that approximately 50% of the EEV-conjugated material escaped the endosome to reach the intracellular disease target as compared to the <2% observed in prior studies of current biologics. While these preclinical studies were not designed as head-to-head comparisons to current biologics, these data generally compare favorably to historical published data regarding the percentage, of current biologics that have been observed to reach their designed intracellular disease target.

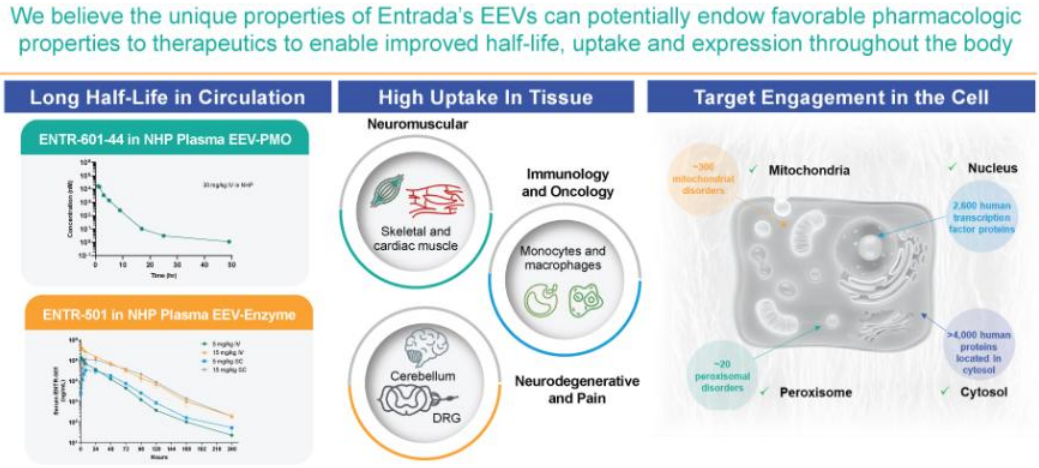


Key attributes of our EEV Platform include:

- **Serum stability and extended half-life:** The cyclic structure of EEVs is designed to limit protease-mediated degradation, resulting in increased stability and extended half-life. In contrast, linear cell-penetrating peptides are rapidly degraded in human serum.

- **Broad biodistribution:** EEVs target phospholipid bilayers and can therefore potentially be delivered to any cell in the body, regardless of route of administration. Additionally, and importantly, cyclization confers unique biophysiochemical properties to EEVs, optimally positioning side chains for membrane association and enabling the use of fewer positively charged cationic residues, which we believe could reduce potential toxicities of EEVs relative to linear peptides which rely on chemistries with a high positive charge.

- **Active uptake and drug release:** EEVs bind to membrane phospholipids but not proteoglycans and thus avoid being trapped in the cell membrane. The low affinity binding to the cell surface triggers endocytosis and we have observed that 90% of the EEV-conjugated material was taken up in tissue in our preclinical studies. The low pH enhanced affinity of EEVs triggers the budding of vesicles from the early endosome and we have observed the subsequent release of approximately 50% of this material into the cytosol in our preclinical studies.

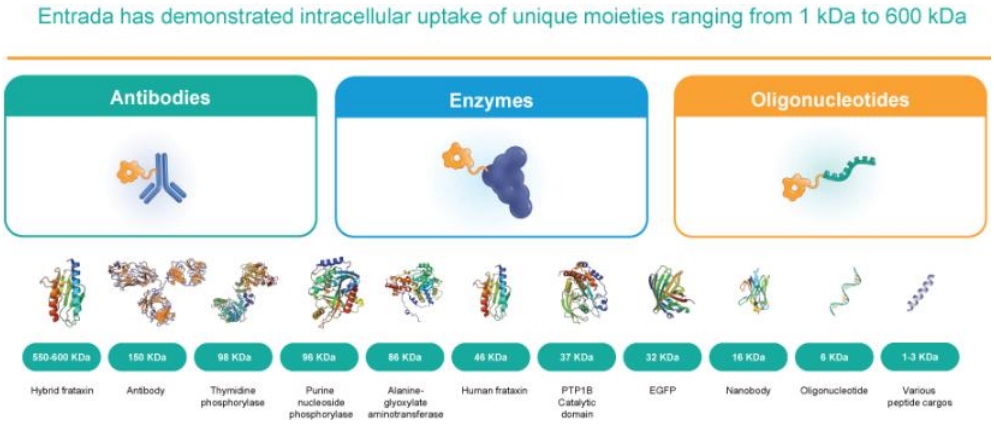


We have developed a proprietary library of EEVs to enable the intracellular engagement of therapeutics against previously inaccessible and undruggable disease-causing targets. EEVs are broadly distributed, highly targeted, designed to have a wide therapeutic index and can be chronically dosed.

Key advantages of our platform include:

- **Broad potential therapeutic index:** Our EEV Platform is designed to allow specific biological therapeutics to engage targets across every cell in the body. In our preclinical studies, we observed that approximately 50% of the EEV-conjugated material escaped the endosome to reach the intracellular disease target as compared to the <2% observed in prior studies of current biologics. While these preclinical studies were not designed as head-to-head comparisons to current biologics, these data generally compare favorably to historical published data regarding the percentage of current biologics that have been observed to reach their designed intracellular disease target. We therefore believe that our EEV Platform can enable greater target exposure with an unconjugated therapeutic and similar dose regimen.

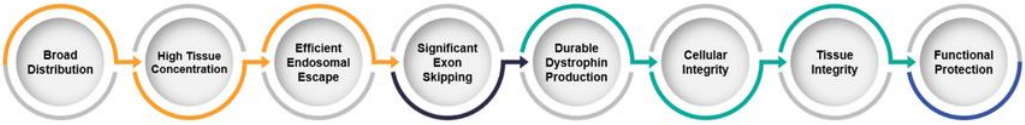
- **Potential across multiple modalities:** Our EEV Platform is designed to enable the development of intracellular therapeutic candidates that modulate, inhibit, degrade or replace an intracellular target to correct the underlying disease pathophysiology. In our preclinical studies of EEVs, we observed intracellular uptake of unique therapeutic candidates ranging in size from 1 kDa to 600 kDa, including oligonucleotides, antibodies and larger multimeric proteins. Unlike viral vectors or certain lipids and nanoparticle constructs, EEVs do not appear to be hampered by “packaging limits”. For example, adeno-associated viruses constructs are limited to 5 kb in length, dramatically restricting both the size of genes and complexity of regulatory sequences that can be delivered. Importantly, our preclinical studies support the concept of modularity in that we can use similar EEV structures across the portfolio. EEVs are then further optimized to the specific application of interest. Each program advanced contributes to a foundation upon which our development portfolio can continue to expand.



- **Potential across tissue types:** Our EEV Platform is not limited to a particular tissue type. Because every cell in the human body is surrounded by a phospholipid bilayer, this enables the systemic delivery of potential therapeutic candidates for a wide range of diseases. We have seen potentially clinically relevant uptake of EEV-PMOs across a wide range of organs, tissue and cell types, including skeletal and cardiac muscle, monocytes and macrophages, and both the cerebellum and dorsal root ganglia. We have also shown in preclinical studies that, if need be, we can target our EEV-conjugated nucleotides by adding tissue-targeting moieties or organelle-targeting sequences, including, for example, nucleus, mitochondria and peroxisome.

- **Multiple delivery routes:** In our preclinical studies, we have generated functional outcomes systemically using IV, IM and SQ injections. Preclinical studies have also demonstrated what we believe to be therapeutically relevant concentrations of product uptake in the cerebellum and dorsal root ganglia via IT administration.

- **Modular approach that enables efficient expansion into multiple therapeutic areas:** We have a wide variety of programs in discovery and preclinical development, including oligonucleotide therapies in rare disease and immunology, antibody-based protein degraders in oncology and enzyme replacement therapy in rare disease. The EEV Platform facilitates the effectiveness of the modality, which in turn produces the translational output.



  - *Oligonucleotide programs:* In our neuromuscular programs, we chemically link EEVs to oligonucleotides . EEV-PMOs are highly programmable and can upregulate or downregulate gene expression. We are developing a potential therapy for patients with DMD as our most advanced lead program. In patients with DMD, there are mutations in or deletions of regions in the genetic code responsible for dystrophin production. These mutations or deletions result in the creation of incomplete RNA sequences, which fail to create functional dystrophin. By using our EEV-PMO, we have demonstrated in animal models that we can skip mutated sequences, allowing the cell to create functional dystrophin. Our second lead program is an EEV-PMO for the treatment of DM1, where we aim to correct mRNA splicing defects associated with muscle tissue development and insulin response to prevent the mistranslation of proteins. We plan to follow this DM1 program with neuromuscular development programs for additional exon skipping amenable populations in DMD and other neuromuscular diseases and in the downregulation of gene expression for a range of non-neuromuscular diseases. The backbone EEV and oligonucleotide chemistries are the same across the various applications, and if successful, we anticipate that we can leverage our approach across a wide range of diseases by simply coding the sequence needed to impact gene expression.

  - *Antibody programs:* Our approach relies on leveraging an EEV-antibody, which binds to a protein of interest. This complex is then marked by an endogenous protein within the cell for degradation, mimicking a way that the body disposes of viral intruders. Preclinical studies have demonstrated intracellular delivery of a variety of full and partial domain antibodies and we have observed target engagement and a meaningful modulation of downstream signaling. Our antibody degraders follow the same basic design, with the only significant change being the antibody sequence needed to target the disease-causing protein of interest.

  - *Enzyme/protein related programs:* EEVs can be linked to an enzyme critical to maintaining specific steps in a cell's metabolic processes. Patients lacking a given enzyme will fail to produce proteins needed to maintain the viability of cells in the body or will suffer a buildup of toxic byproducts, either of which can result in disease and potentially death. We have generated a number of EEV-enzyme conjugates, including ENTR-501 for MNGIE, a fatal mitochondrial disease, for which we have completed IND-enabling studies. NHP pharmacokinetic and acute and chronic toxicology studies indicated both a long circulating half-life and a favorable tolerability profile, which may serve as a foundation upon which our ERT programs can later build. We are also exploring the use of EEVs as a novel non-viral vector for the delivery of CRISPR-Cas to enable highly efficient approaches to gene editing.

- **A simple and scalable construct designed to translate from preclinical to clinical development across our therapeutic programs:** EEVs are comprised of small serum-stable cyclic peptides of approximately 10 amino acid residues or fewer produced via synthetic chemistry.

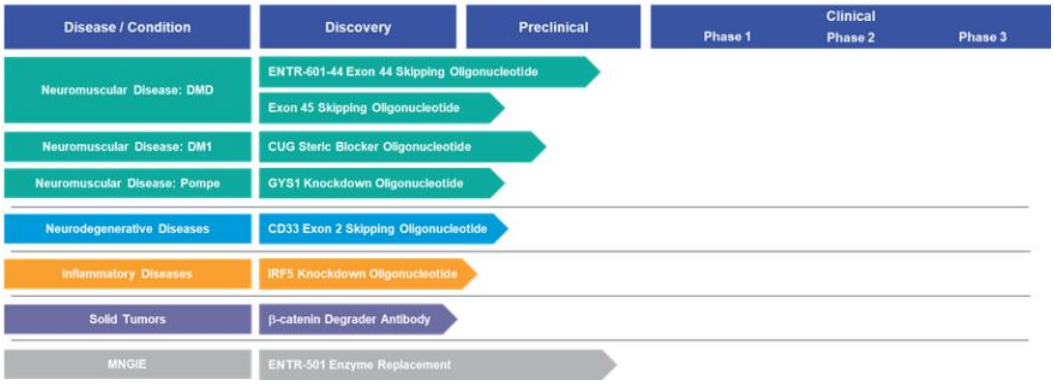
  - EEVs have been manufactured efficiently to clinical scale and, because we use well-understood chemical conjugation methods to link EEVs to our oligonucleotides, antibodies and enzymes of interest, we believe manufacturing the final drug product can be optimized. We have experience manufacturing an EEV therapeutic candidate, ENTR-501, under Good Manufacturing Practices (GMP).

- The size of EEVs implies that they are unlikely to be presented on the surface of immune cells, and therefore we believe the risk of immunogenicity is low and limited to the conjugate of the EEV therapeutic candidate.

Ultimately, we believe that the significant increase in intracellular target exposure enabled by EEV conjugation has the potential to translate into substantial improvements to the efficacy, safety, tolerability, manufacturability and cost of future medicines.

Our Development Portfolio

We are leveraging our EEV Platform to create a diverse and expanding development portfolio of oligonucleotide-, antibody- and enzyme-based programs. Included in this development portfolio are several of our oligonucleotide programs for the treatment of multiple neuromuscular diseases, including DMD, DM1 and additional preclinical and discovery programs. In addition, we are exploring oligonucleotide opportunities in immune mediated diseases and oncology. The development portfolio also includes antibody based intracellular protein degradation programs for oncology. Research efforts include enzyme replacement therapies, targeting moieties and CRISPR-Cas. The chart below represents a summary of our initial development programs, each of which are wholly owned.



Neuromuscular Diseases

Duchenne Muscular Dystrophy

We are initially focused on the development of disease-modifying treatments for patients with DMD. We are developing therapeutic candidates to address the genetic basis, at the exon-specific level, of DMD. EEV oligonucleotides are designed to promote the skipping of exon mutations associated with DMD, enabling muscle cells to create a functional dystrophin at a level that we believe may slow, stop or even reverse DMD progression.

We are prioritizing the development of an EEV-PMO, ENTR-601-44, for patients with DMD that are exon 44 skipping amenable. This patient population represents approximately 7.6% of patients with DMD with substantial unmet medical need, due to the lack of approved disease-modifying therapies available. Furthermore, there are also no ongoing clinical trials for patients with DMD that are exon 44 skipping amenable in the United States or Europe, and we believe we have the potential to be first to market. We believe that the high unmet need combined with the lack of alternative therapeutics will support rapid clinical trial enrollment.

We are also developing an EEV-PMO for patients with DMD that are exon 45 skipping amenable, who account for approximately 8% of patients with DMD. In the United States alone, there is currently only one product approved for patients amenable to exon 45 skipping, which has demonstrated an increase in dystrophin of less than 2% in clinical trials. The product has not yet demonstrated a clinical benefit in confirmatory trials, which are ongoing. We plan to leverage our preclinical and regulatory experience with the ENTR-601-44 program in developing the EEV-PMO candidate, given the substantially similar preclinical and clinical development paths of these therapeutic candidates, with the goal of efficiently advancing this program.

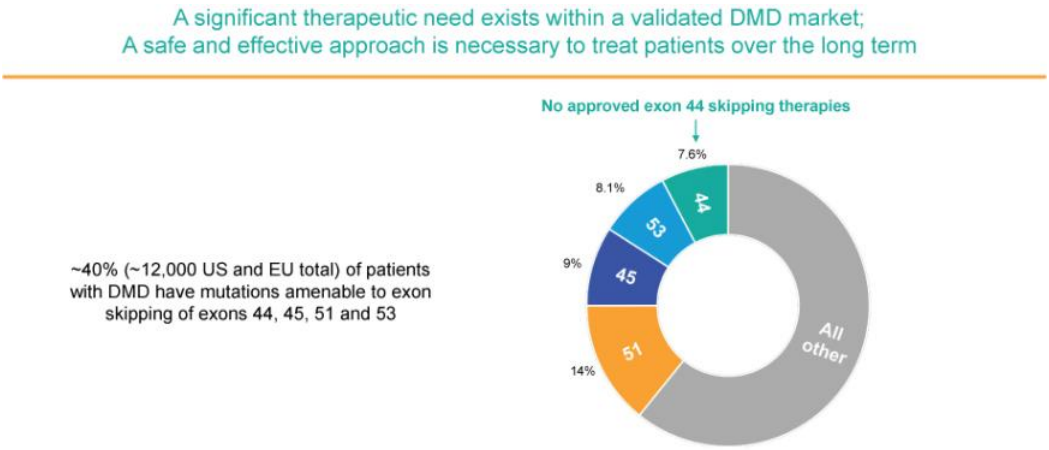
We plan to submit an IND to the FDA for ENTR-601-44 in 2022 and, pending authorization to proceed from the FDA, to report initial clinical data in 2023, and to advance a potential EEV-PMO candidate for patients with DMD that are exon 45 skipping amenable thereafter.

DMD Background and Market Opportunity

DMD is a monogenic, X-linked disease caused by mutations in the DMD gene, which encodes for the dystrophin protein. Dystrophin is essential to maintaining the structural integrity and normal function of muscle cells for walking, breathing and cardiac function. In patients with DMD, mutations in the DMD gene can lead to certain exons being misread, resulting in a failure to produce sufficient functional dystrophin. The reduction or absence of functional dystrophin leads to damage to muscle cell membranes, resulting in muscle cell death and progressive loss of muscle function.

The symptoms of DMD typically manifest in the first few years of life. Patients experience progressive muscle weakness and muscle wasting and have difficulty standing up, climbing stairs, running, breathing and performing daily functions. As the disease progresses, the severity of damage to skeletal and cardiac muscles results in most patients experiencing total loss of ambulation in the pre-teenage or early teenage years. Progressive loss of upper extremity function is often observed in the mid-to-late teens followed by paralysis, respiratory and/or cardiac failure, resulting in early mortality in the third or fourth decade of life.

We estimate that DMD occurs in approximately one in every 3,500 to 5,000 patients and that the patient population is approximately 30,000 patients in the aggregate in the United States and Europe. Approximately 80% of patients have mutations amenable to exon skipping in the nucleus. Approximately 40% of patients with DMD have mutations amenable to exon skipping of exons 44, 45, 51 and 53, as illustrated in the figure below.



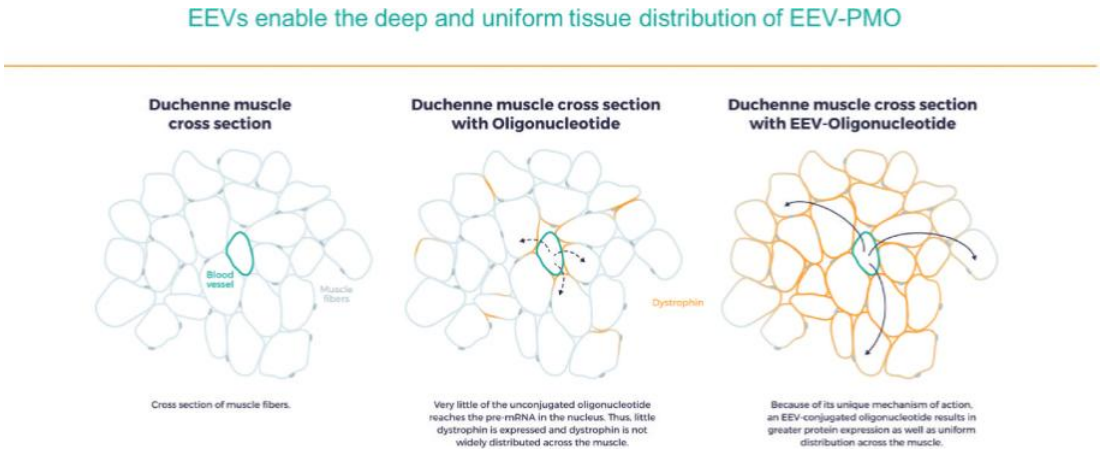
Current Treatment Landscape and Limitations

Corticosteroids are the current standard of care. However, chronic use of corticosteroids, particularly in pediatric populations, is challenging due to side effects including growth impairment, immune suppression, obesity and other endocrine-related disorders. There are four FDA-approved PMO-based oligonucleotide skipping therapies, each addressing a specific mutation: casimersen (exon 45), eteplirsen (exon 51), golodirsen (exon 53) and viltolarsen (exon 53). These products have all been approved using the accelerated approval pathway on the basis of dystrophin production. Currently approved exon skipping therapeutics have demonstrated a modest improvement in dystrophin levels ranging from approximately 1-6%. However, the FDA-approved labels for all four drugs state that continued approval may be contingent upon the verification of a clinical benefit in confirmatory clinical trials. None of the products are approved by the European Medicines Agency due to insufficient evidence of clinical benefit. A fifth drug, ataluren, has only been conditionally approved outside of the United States in certain territories for nonsense mutations in ambulatory patients with DMD aged five years and older. Finally, these therapies require weekly intravenous infusions which is suboptimal from a patient perspective. In summary, each of these approved products also seeks to address DMD through exon skipping, but to date, the clinical benefits of these products have not been confirmed.

Our Solution

Our DMD program is designed to address the genetic basis of DMD by promoting the skipping of specific DMD exons in the nucleus, allowing muscle cells to create a functional dystrophin protein. Our EEV Platform is designed to enable high cellular uptake and robust cytosolic delivery of EEV therapeutic candidates, resulting in a greater amount of the oligonucleotide being able to reach its intended target in the nucleus. Based on preclinical data, we have shown that our proprietary oligonucleotide is then able to promote enhanced exon skipping and dystrophin production.

In preclinical models, we have observed that conjugation of an oligonucleotide to our EEV results in multi-fold greater exon skipping and dystrophin production than the oligonucleotide alone, with such results indicating dystrophin production comparable to wild-type levels in certain tissues. We have observed substantial improvement in dystrophin production in both skeletal and cardiac muscle, as well as uniform dystrophin production within tissues that we believe may be attributable to the unique mechanism of action of our EEV Platform and the broad biodistribution of our oligonucleotide conjugates. We have observed deep and uniform penetration of EEV-PMOs as compared to unconjugated oligonucleotides in our preclinical models, as illustrated below.



Importantly, we believe an increased level of dystrophin production in the heart may translate to improved cardiac function in patients with DMD.

Our preclinical data have demonstrated 50% to 100% correction of exon skipping in the D2-mdx model, which mimics human disease, and in a human dystrophin mouse model which enables us to evaluate our lead sequence directly. In an initial NHP model, we have observed almost 90% target exon skipping in skeletal muscles. We have generated promising *in vivo* data in cardiac and skeletal muscles (including the diaphragm) across a range of disease and wild-type models (both murine and NHP). We believe the observed increase in dystrophin production is sufficient to protect muscle from progressive functional decline in treated mice and the improvement in functional outcomes versus controls observed in the D2-mdx model supports this belief.

Summary of Preclinical Data

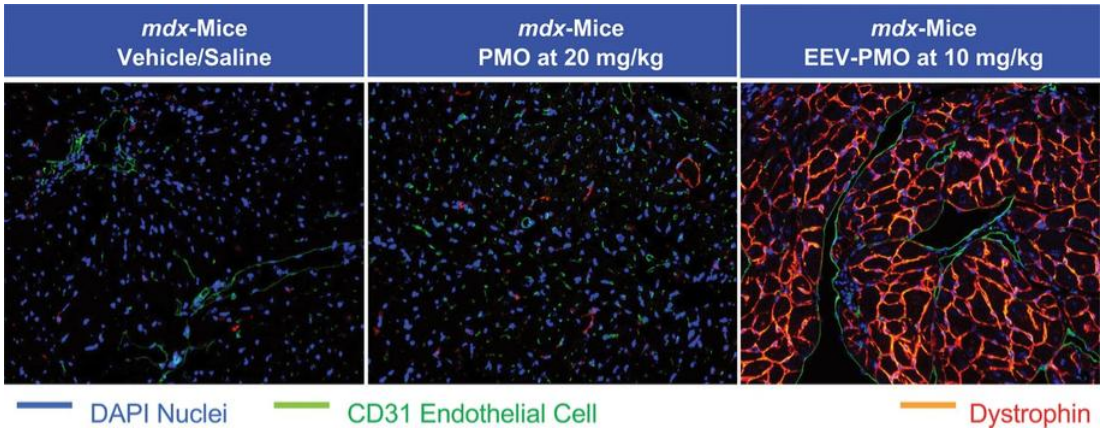
Our early data in mouse and NHP models have been consistent and robust. We have observed substantial exon skipping and dystrophin production in various tissues of mdx mice. The mdx mouse is the canonical model used in DMD research and carries a spontaneous nonsense mutation in exon 23 of the DMD gene. Although this does not allow for the testing of oligonucleotides specific to human mutations, it does enable measurement of tissue concentration of oligonucleotides, exon 23 skipping levels and the corresponding dystrophin production. This allowed us to extrapolate anticipated dystrophin production from exon-skipping observations as we move to NHP models. We were also able to show in both single-dose and multiple-dose experiments that the EEV-PMOs has greater activity than unconjugated PMOs. Similarly, EEV-PMOs had greater activity than alternative cell-penetrating peptide conjugates in our preclinical studies. We also observed corresponding and significant improvements in functional outcomes as measured in the exon 23 specific D2-mdx mouse. In particular, we observed meaningful tissue uptake and exon skipping, ranging from

approximately 60% to 95% depending on the tissue In this model, EEV-PMO treated tissues have substantial restoration of both dystrophin and alpha sarcoglycan. Our preclinical studies have also demonstrated reductions in serum CK to wild-type levels in D2-mdx model. Serum CK is a commonly-used biomarker of systemic muscle breakdown. Correction of CK is believed to be a strong indicator of pharmacodynamic activity and a marker of muscle integrity restoration. Finally, we observed extended half-life and high levels (almost 90% in the biceps) of exon skipping in a NHP with ENTR-601-44.

In the data below, unless otherwise noted, we used reverse transcription-polymerase chain reaction to assess exon skipping and Western Blot to assess dystrophin production. Our preclinical studies have demonstrated durable dystrophin production over a period of up to eight weeks, suggesting the possibility of infrequent dosing. Immunohistochemistry and morphometric analysis confirm that the protein is broadly distributed across tissues, which is necessary if the muscle is to maintain function.

For each of our preclinical studies that were powered for statistical significance, we have so indicated with the p or p-values presented. In the description of our preclinical studies below and elsewhere in this prospectus, p or p-values represent the probability that random chance caused the result. For instance, a p-value of 0.001 means that there is a 0.1% probability that the difference between the placebo group and the treatment group is purely due to random chance. A p-value of less than or equal to 0.05 is a commonly used threshold for identifying statistically significant outcomes. Except with respect to ENTR-501, our preclinical studies to date have not been designed as toxicology studies and therefore we have not collected safety data from such studies. We plan to conduct toxicology studies in compliance with Good Laboratory Practices in advance of submitting an IND for any of our therapeutic-candidates.

mdx Mouse Dystrophin Distribution Analyzed via Immunofluorescence After Four Injections of EEV-PMO at 10 mg/kg

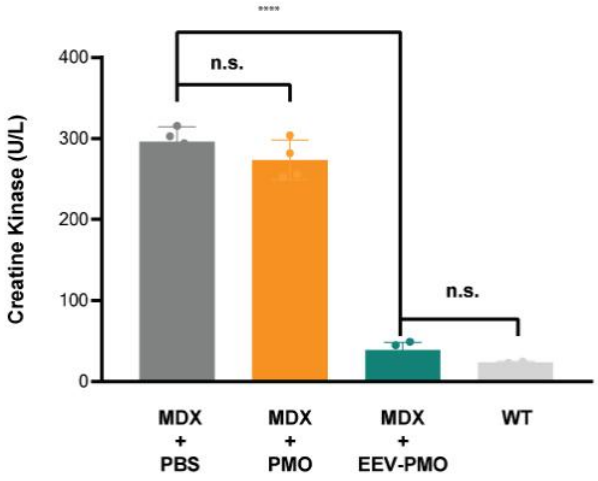


In the experiment above, mdx mice were injected with weekly doses of either saline, unconjugated exon 23 skipping PMO or an EEV conjugated to the same exon 23 skipping PMO over the course of four weeks. Samples were taken one week after the fourth dose. The EEV-PMO-DMD substantially increased dystrophin production and accumulation in the heart, with approximately 40% of the cardiac tissue staining positive for dystrophin (in red). This compares favorably to the PMO alone, where at even double the dose virtually no dystrophin can be seen. Endothelial cells are stained green, and as shown in the image, dystrophin can be observed distributing broadly and deep into the cardiac tissue. We believe this experiment suggests that at low doses an EEV oligonucleotide has the potential to substantially improve on treatment with unconjugated oligonucleotides. We also believe these heart results suggest the possibility that EEV-PMOs may address cardiomyopathy in patients with DMD, which is a major complication and leading cause of death associated with the disease. We believe this could therefore potentially improve survival rates.

This improvement in dystrophin production at 10 mg/kg is also associated with an observed improvement in measured serum creatin kinase (CK) levels. Serum CK is a commonly-used biomarker for systemic muscle breakdown. CK is released from muscles with damaged and porous sarcolemma, which, in the case of DMD, is due to a lack of

functional dystrophin. Normalization of serum CK indicates broad correction of dystrophin and protection of the sarcolemma throughout the body, which can further imply a potential restoration of function.

Normalization of Serum CK Levels in mdx and Wild-Type (BL10) Mice

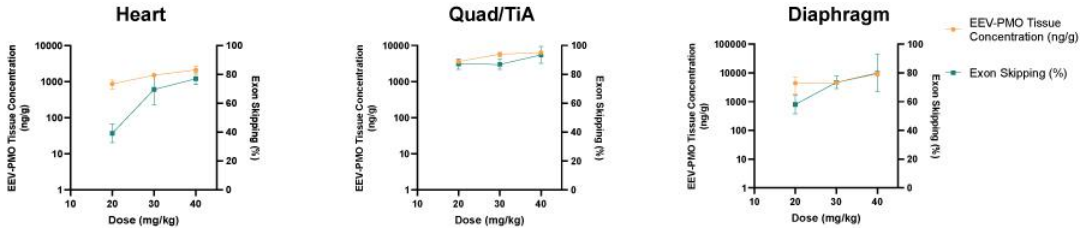


*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

In the experiment above mdx mice were injected with weekly doses of either saline, unconjugated exon 23 skipping PMO or an EEV conjugated to the same exon 23 skipping PMO over the course of four weeks. Samples were taken one week after the fourth dose.

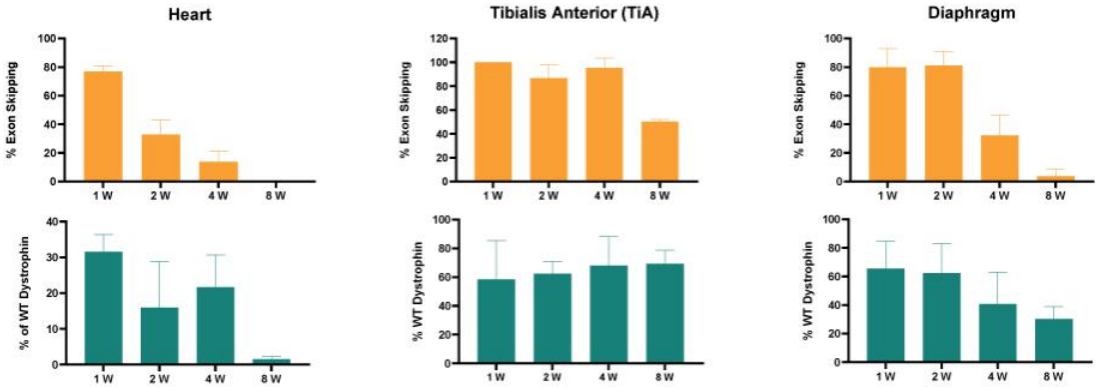
We have also observed that tissue concentration of EEV-PMO in the cell correlates with the level of exon skipping, which correlates with dystrophin production.

High Levels of Exon 23 Skipping and Tissue Concentration Observed in Various Muscle Groups at Three Different Doses of EEV-PMO in mdx Mice



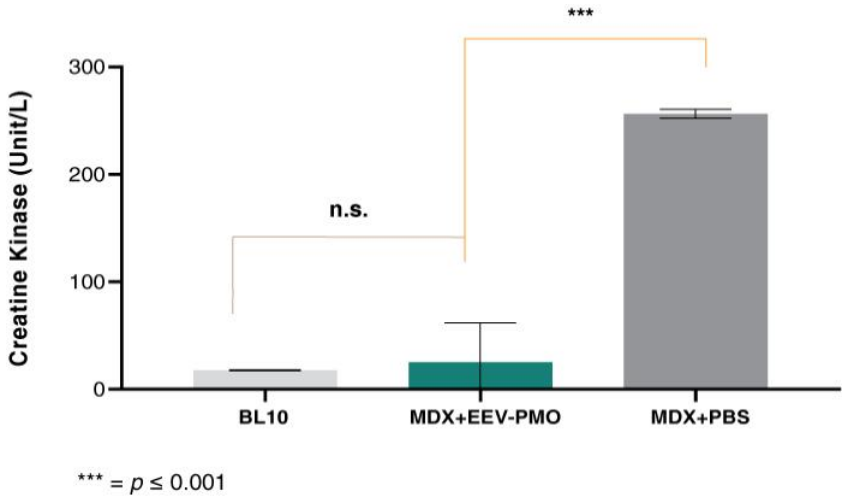
In the mdx mouse model illustrated above, exon skipping and tissue concentration in various muscle groups have been quantified one week after a single 20, 30 or 40 mg/kg intravenous (IV) dose of an EEV conjugate to an exon 23 skipping PMO in mdx mice. A dose-dependent effect was seen, both with respect to tissue concentrations and exon 23 skipping levels, which ranged from approximately 80%-100% at the highest IV dose of 40 mg/kg, depending on the tissue sampled. These dose-dependent tissue concentrations and the correlation with exon skipping suggest active target engagement in heart, diaphragm and other skeletal muscles.

High Levels of Exon 23 Skipping and Dystrophin Correction Observed up to 8 Weeks After a Single IV Dose of EEV-PMO in mdx Mice



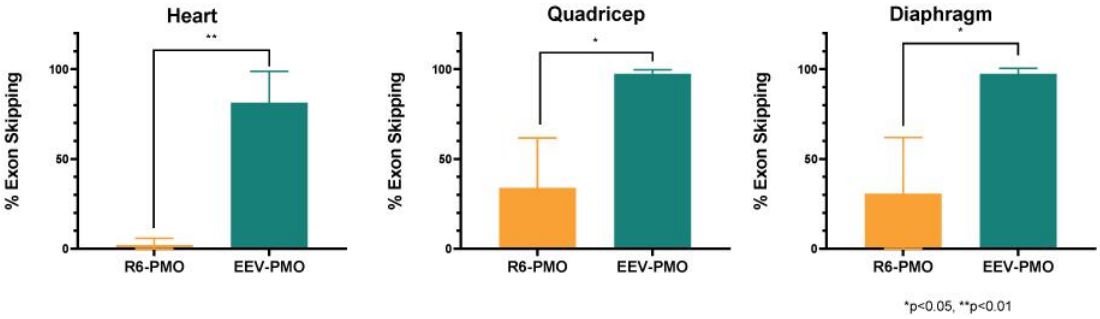
Following dose-ranging experiments, exon 23 skipping and dystrophin production in various muscle groups were quantified one week, two weeks, four weeks and eight weeks after a single IV dosage of 40 mg/kg in mdx mice. We selected the highest dose based on the magnitude of exon skipping observed.

Normalization of Serum CK Levels in mdx and Wild-Type (BL10) Mice



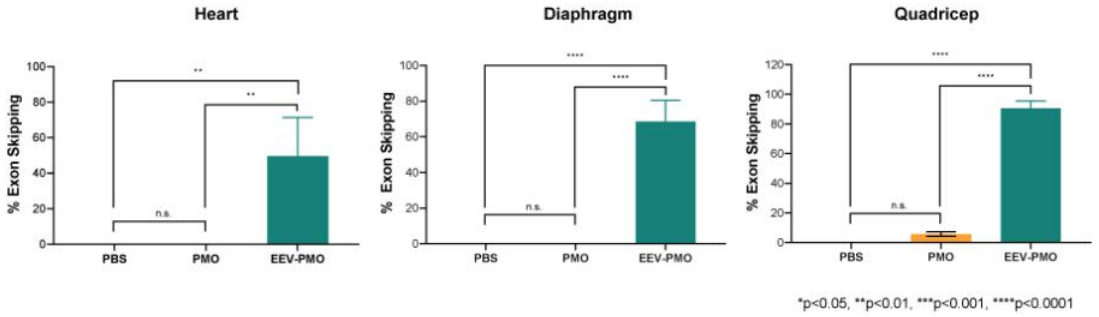
In this experiment, untreated wild-type (BL10) mice were compared to mdx mice treated with EEV-PMO and mdx mice treated with phosphate-buffered saline (PBS). Serum CK from mdx mice was analyzed one week after a single 40 mg/kg IV dose of EEV-PMO skipping exon 23 or of PBS. Treatment with EEV-PMO normalized serum CK levels in the mdx mice, suggesting restoration of muscle integrity. In contrast, no significant correction of serum CK was seen in the PBS control arm.

EEV-PMO Significantly Improved Exon 23 Skipping After 3 Days in mdx Mice as Compared to R6-PMO



To compare the exon 23 skipping of an EEV against an alternative published linear peptide, we synthesized a 6 arginine (R6) cell-penetrating peptide and conjugated it to the exon 23 skipping oligonucleotide. We then compared the activity of this molecule to EEV-PMO, by conjugating the same oligonucleotide to one of our EEVs. After a single 40 mg/kg IV dose of the EEV-PMO or the R6-PMO, the EEV-PMO exhibited profound effects, with near complete exon skipping in the diaphragm and the quadriceps and approximately 60% exon skipping in the heart. The R6-PMO results were very limited in the skeletal muscle and virtually no pharmacodynamic effects were seen in the heart.

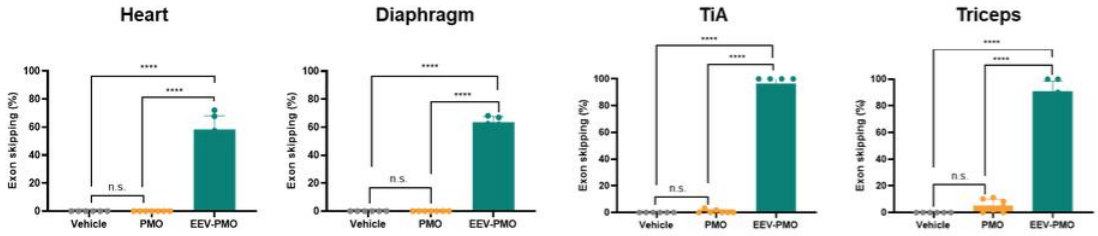
Superior Correction of Exon 23 Skipping in the D2-mdx Model Versus Unconjugated PMO



We have employed a methodical and robust approach to candidate qualification by generating data in the canonical mdx mouse, as well as in a mouse model with a more severe phenotype known as the D2-mdx mouse. While the approach remains focused on exon 23 skipping, the D2-mdx mouse model more closely represents human disease as these animals develop more inflammation, fibrosis and exhibit less muscle regeneration over time when compared to the mdx model. In the study above, we compare exon skipping in the quadriceps, diaphragm and heart as generated by either the EEV-PMO skipping exon 23 or the PMO alone skipping exon 23. The lack of response from unconjugated PMO illustrates the difficulty in generating pharmacodynamic responses in the D2-mdx model, and further reinforces the importance of EEV conjugation. The animals were given a single 40 mg/kg IV dose of either the PMO or the EEV-PMO. We were able to demonstrate approximately 50% to 95% exon skipping from the mice dosed with EEV-PMO, depending on the tissue sampled.

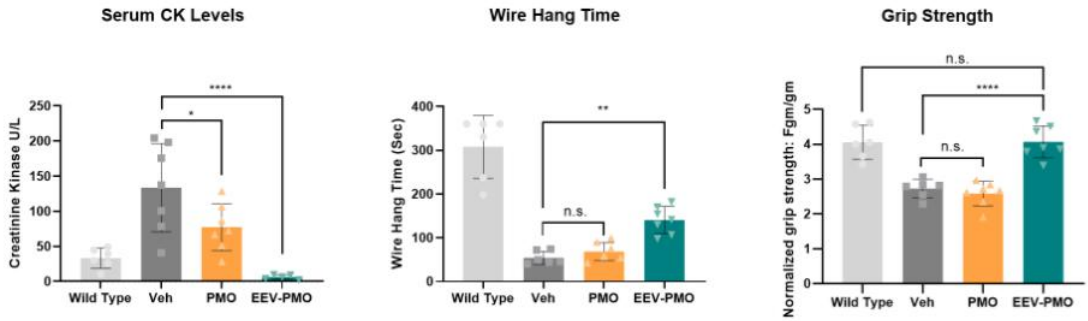
Subsequent to the single dose study above, a separate repeat dose study was conducted as shown below. D2-mdx mice were treated with three IV doses at monthly intervals of either 20 mg/kg of a saline vehicle, PMO-23, or EEV-PMO-23 (n=6 per cohort). We compared exon skipping by one-step reverse transcription-polymerase chain reaction in the heart, diaphragm, tibialis anterior (TiA) and triceps as generated by either the EEV-PMO-23 skipping exon 23 or the PMO-23 alone skipping exon 23. We believe the significant difference in exon skipping observed between the EEV-PMO-23 and the PMO-23 in the D2-mdx model at a lower dose further reinforces the potential importance of EEV conjugation. We were able to demonstrate approximately 60% to over 95% exon skipping from the mice dosed with EEV-PMO-23 depending on the tissue sampled.

Superior Correction of Exon 23 Skipping at 22 Weeks Using an EEV-PMO in the D2-mdx Model Versus an Unconjugated PMO At 20 mg/kg



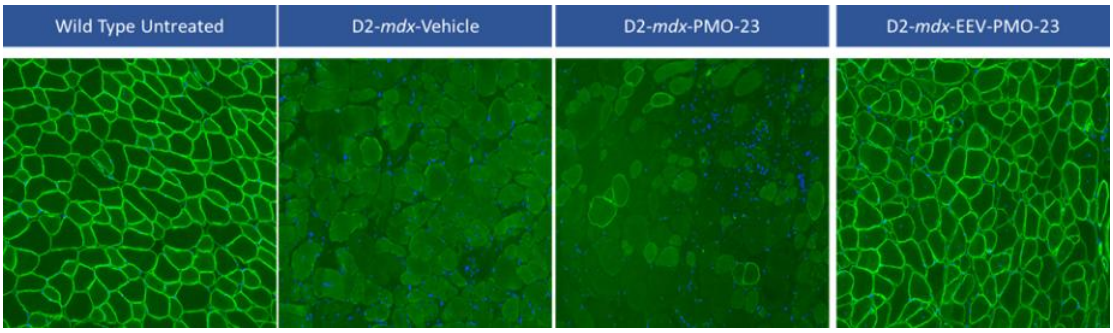
A durable CK response was observed in EEV-PMO-23 treated mice versus both vehicle and PMO-23 treated mice. In this experiment D2-mdx mice were treated with 4 monthly doses of either vehicle, 20 mg/kg PMO or 20 mg/kg PMO equivalent of EEV-PMO, and the data were collected 4 weeks after the last dose. No significant difference was seen between CK levels measured in wild type control mice and EEV-PMO-23 treated mice. We believe that this observation of reduced skeletal muscle breakdown resulted in improved functional outcomes for EEV-PMO-23 treated mice as evidenced by measurement of both wire hang time and a normalization of grip strength. In each case a significant difference ($p<0.05$ for wire hang time, $p<0.001$ for grip strength) between PMO-23 treated mice and EEV-PMO-23 treated mice was observed.

Repeat EEV-PMO-23 Treatment Normalized Serum CK Levels and Showed Significant Improvements in Muscle Function When Compared to PMO Alone After Four Monthly IV Doses in D2-mdx Mice



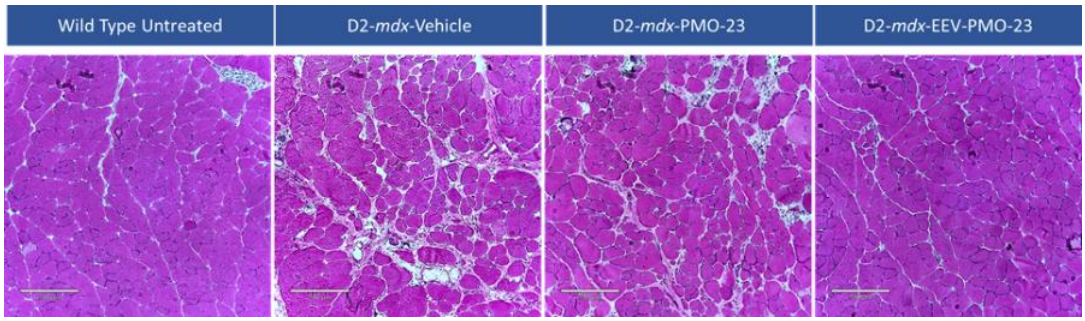
In the same experiment, dystrophin expression was assessed four weeks post last injection via immunofluorescent staining, shown in the representative gastrocnemius sections shown in bright green below. The untreated wild type mice and the EEV-PMO-23 treated D2-mdx mice show broad and appropriate dystrophin expression, while the D2-mdx mice treated with vehicle control and the D2-mdx animals treated with PMO-23 show little to no dystrophin expression.

D2-mdx Mouse Dystrophin Expression Analyzed via Immunofluorescence Is Enhanced After IV Administration of EEV-PMO Versus PMO Alone at 20 mg/kg



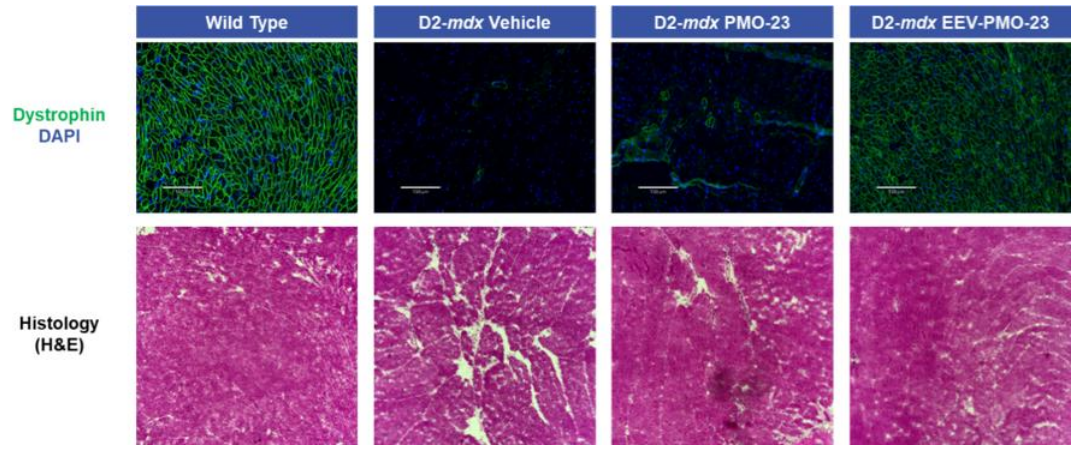
Muscle histopathology was also assessed four weeks after the last injection. The D2-mdx animals treated with vehicle control and those treated with PMO-23 show clear signs of fibrosis and muscle damage. This stands in contrast to healthy samples from both the normal, wild type mice and the EEV-PMO-23 treated D2-mdx mice shown on the far left and far right panels below.

Correction of D2-mdx Mouse Histopathology is Enhanced after IV Administration of EEV-PMO Versus PMO Alone at 20 mg/kg



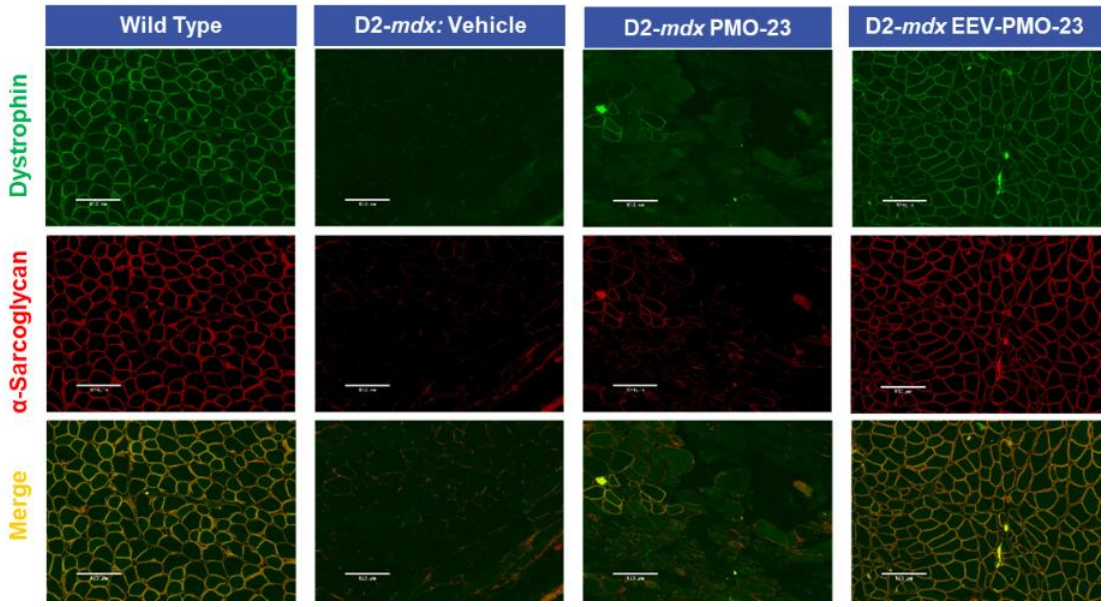
In the same experiment we also observed similarly dramatic results when comparing the wild type, control and treated images of both dystrophin and histology in the heart, as shown below.

Repeat EEV-PMO-23 Treatment Corrected Dystrophin Expression and Pathology in the Heart After Four Monthly IV Doses in D2-mdx Mice



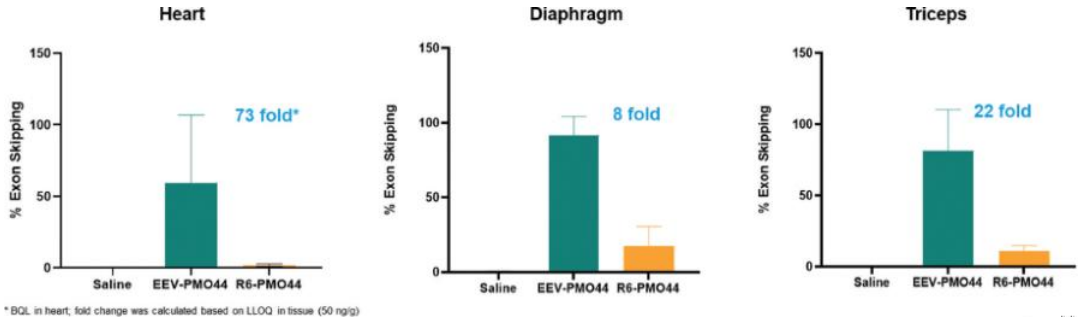
Further analysis of the previous experiment showed EEV-PMO treated tissues have almost normalized the level and the localization of both dystrophin and α-sarcoglycan. In striated muscle, sarcoglycans interact with dystrophin and other dystrophin-associated proteins to form the dystrophin-associated glycoprotein complex which protects the sarcolemma from contraction-induced injury. In the absence of dystrophin, α-sarcoglycan fails to correctly localize to the dystrophin-glycoprotein complex (DGC) causing weakening of the plasma membrane. Loss of dystrophin leads to loss in alpha-sarcoglycan in the D2-*mdx* tissue. In the figure below PMO treated mice had limited restoration of dystrophin as well as a-sarcoglycan. In contrast, EEV-PMO treated tissues have almost complete restoration of both dystrophin and alpha-sarcoglycan.

Repeat EEV-PMO-23 Treatment Resulted in Functional Restoration of Dystrophin and DGC Protein α-sarcoglycan After Four Monthly IV Doses in D2-mdx Mice



The mdx mouse model, the most commonly used mouse model for DMD, carries a spontaneous nonsense mutation in exon 23 of the DMD gene. While this model has been useful to show proof-of-concept of the exon skipping approach *in vivo*, it does not allow for the testing of human-specific oligonucleotides. Consequently, we also used transgenic mice carrying an integrated copy of the full-length human DMD gene with an exon 44 skipping amenable mutation. While these mice do not exhibit the DMD phenotype, the model does allow for an assessment of exon skipping levels. The mice were given a single IV dose of an EEV conjugated to an exon 44 skipping PMO (a combination thereof defined as EEV-PMO-44) at 15 mg/kg and near 100% exon skipping was observed. This result is notable because the mice in this model have intact muscle cells, which have historically been more difficult for therapeutics to access than the damaged cells seen in a mdx model. We believe that these robust exon skipping results suggest the potential for our EEV-PMO to expand into additional neuromuscular diseases in which uptake into intact muscle is crucial to demonstrating clinical activity.

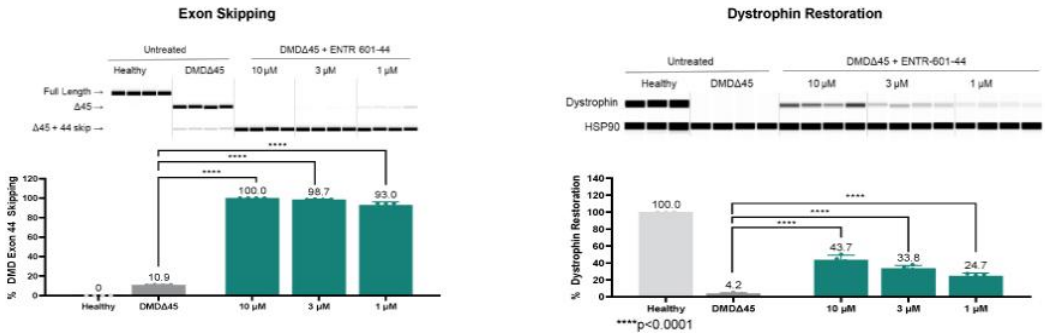
Exon 44 Skipping Activity of EEV-PMO-44 as Compared to a R6 Conjugated Exon 44 Skipping PMO (Single IV Dose of 15 mg/kg in hDystrophin Mice)



We conjugated our lead exon 44 skipping sequence to an EEV from our candidate library, which we refer to as EEV-PMO-44, as mentioned above. Human dystrophic mice were IV dosed with 15 mg/kg of either EEV-PMO-44 or a R6 linear peptide conjugated to the same exon 44 skipping PMO. We observed exon skipping of between 60% to approximately 95% in the EEV-PMO-DMD-44 mice, compared to exon skipping of less than 20% in the R6-PMO-44-dosed mice.

Following the exon 44 skipping preclinical work depicted above, we completed lead optimization work and initiated experiments for ENTR-601-44 in patient derived cells, humanized mice, and NHPs. The results of these studies are described below.

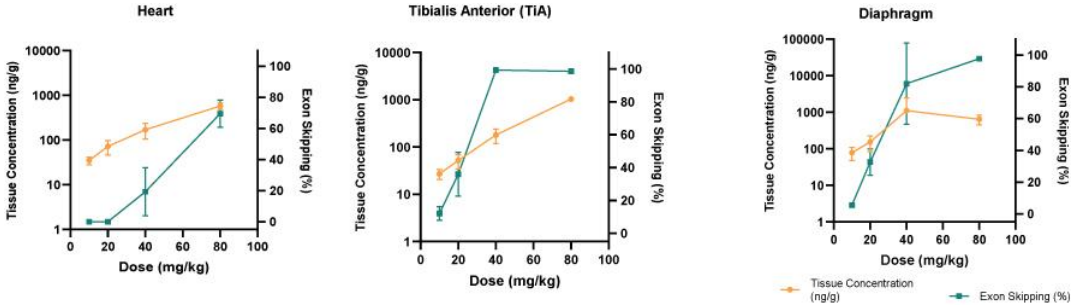
Dose-Dependent Levels of Exon Skipping and Significant Dystrophin Restoration Observed in Patient Derived Cells Treated With ENTR-601-44



In the experiment depicted above, patient derived cells were treated with the EEV-PMO-44, or ENTR-601-44. Dose-dependent exon 44 skipping and dystrophin protein restoration was observed (up to 100% and 43.7% respectively) in DMD patient-derived muscle cells treated with ENTR-601-44 compared with both untreated patient derived cells and

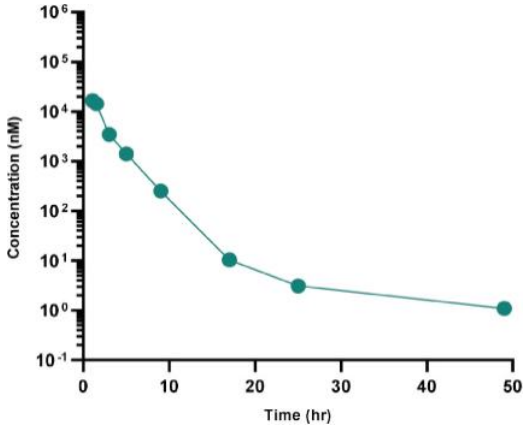
healthy cells. ENTR-601-44 was then studied in the humanized mouse model to assess uptake in tissue and exon skipping potential.

ENTR-601-44 Associated Dose (IV)-Dependent Tissue Exposure and Exon Skipping in a Transgenic Murine Model Carrying the Full-Length Human DMD Gene



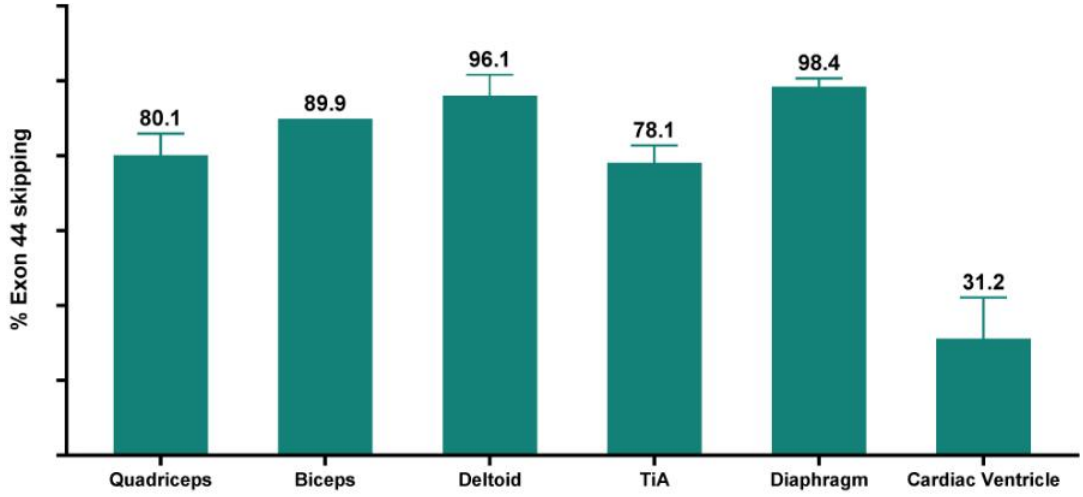
In this experiment, the transgenic mice carrying an integrated copy of the full- length human DMD gene were administered ascending IV doses of ENTR-601-44 at various levels ranging from 10 mg/kg to 80 mg/kg. Exon skipping and tissue exposure were each assessed five days after dosing. We observed dose dependent levels of tissue exposure of up to 80% and exon skipping up to 100% with translationally relevant doses. Following the results from our transgenic mouse study, we initiated studies in NHPs.

Extended Circulating Half-Life for ENTR-601-44 Observed in Non-Human Primate Model



In the study depicted above, an IV dose of 30 mg/kg was administered over the course of one hour. The NHP was assessed at regular intervals, and an extended circulating half-life was observed. ENTR-601-44 was detectable in plasma up to 50 hours later. This pharmacokinetic profile suggests an opportunity for intended tissue exposure, target engagement and pharmacodynamic effects.

Meaningful Levels of Exon Skipping Observed After 7 Days in NHP after IV Administration of ENTR-601-44 at a dose of 30 mg/kg



A single 30 mg/kg IV dose of ENTR-601-44 resulted in meaningful levels of exon skipping in both skeletal and heart muscles. These levels of exon skipping appear to correlate with the exon skipping observed with ENTR-601-44 in the transgenic mouse and the exon 23 skipping observed in the mdx and the D2-mdx mouse. We believe that these data, together with the correlation between exon skipping and dystrophin production in PPMO clinical trials, are encouraging in the translational potential of ENTR-601-44. We further believe that these data provide support for the potential of the EEV Platform to address additional DMD populations. We expect to complete GLP toxicology studies to support an IND filing in the second half of 2022.

Clinical Development Plan

We plan to study our ENTR-601-44 in healthy adult volunteers initially and leverage the regulatory precedents set by exon skipping programs both in the clinic and on the market in the United States. We plan to initiate ascending dose studies, beginning with a single ascending dose in healthy volunteers, to assess safety and tolerability as well as evaluate pharmacokinetics (PK), and potentially exon skipping at the highest doses tested. Pending the outcome of these studies, and subsequent regulatory feedback we plan to initiate an MAD/Phase 2b study, in which we intend to assess tolerability, safety and PK in the ascending dose portion of the study. We expect the MAD/Phase 2b study will measure changes in dystrophin levels as the primary endpoint, and a variety of clinical measures as secondary endpoints. We also plan to conduct exploratory assessments of cardiac and pulmonary function as part of this study. We plan to study a second program for patients with DMD that are exon 45 skipping amenable and follow a similar clinical development plan. We believe that generating clinical proof-of-concept in these underserved populations will create translational, regulatory and clinical development synergies, and improve our potential to create meaningful treatment for these patients and those patients with DMD that are exon 51 and exon 53 skipping amenable.

We plan to submit an IND to the FDA for ENTR-601-44 in the second half of 2022 and, pending authorization to proceed from the FDA, to report initial clinical data in 2023. We plan to submit an IND to the FDA for a potential EEV-PMO candidate for patients with DMD that are exon 45 skipping amenable thereafter.

DM1

DM1 is a rare disease, commonly estimated to affect over 40,000 people in the United States and over 50,000 in Europe. The disease is caused by a mutation driven alteration of normal RNA structure manifesting as an increase in the number of CTG triplet repeats found in the 3’ non-coding region of the DM1 protein kinase (DMPK) gene. The number of repeats ranges from up to approximately 35 copies in healthy individuals to many thousands in patients with DM1. The resulting transcripts, which contain an expanded CUG tract, aggregate in discrete foci in the nuclei of DM patient cells. The excessive number of CUG repeats form large hairpin loops that entrap the DMPK pre-mRNA in the nucleus

and impart toxic activity, referred to as a toxic gain-of-function. Specifically, mutant DMPK pre-mRNA sequesters a critical CUG-binding protein, muscle blind-like protein 1 (MBNL1), forming nuclear foci and inhibiting its ability to perform its normal function of guiding pre-mRNA processing of gene transcription for many other genes. These genes, among others, include insulin receptor signaling (INSR), Ras receptor signaling which is implicated in cell growth (SOS1), Bridging Integrator-1 (BIN1) which is implicated in cardiac development, and LIM domain binding 3 (LDB3) which plays a role in stabilizing the sarcomere (the basic units of muscles) during contraction. As a result, multiple pre-mRNAs that encode key proteins are misprocessed and this contributes to the multisystemic nature of the disease. These abnormal proteins ultimately cause DM1. The progression of DM1 may depend on the growth of the expanded repeat over time, suggesting that stabilization of the repeat is a means to postpone the onset or slow the progression.

DM1 is typically categorized based on age of onset and severity of symptoms into various phenotypes: 75% classical (adult-onset in the second to fourth decade of life); 10% childhood; and 15% congenital. All forms of DM1, except the late-onset form, are associated with high levels of disease burden and in the most severe cases can be associated with premature mortality. Life expectancy ranges from 45 years to 60 years. Seventy percent of early mortality is caused by cardiorespiratory complications. Respiratory failure due to muscle weakness (especially diaphragmatic weakness) causes at least 40% of early mortality, and cardiac abnormalities account for approximately 30%. The clinical course of DM1 is usually slowly progressive, but may become extremely disabling, especially when more generalized limb weakness and respiratory muscle impairment develops. Systemic manifestations such as fatigue, gastrointestinal (GI) complications, cataracts, incontinence and excessive daytime sleepiness greatly impact a patient’s quality of life. As a result, DM1 leads to physical impairment, activity limitations and decreased participation in social activities and work.

Current Treatment Landscape and Limitations

There are currently no approved therapies to treat DM1 and treatment is focused largely on symptom management, which is tailored to the system affected and can therefore range from diet modification and physical therapy to surgery and ventilatory support. A previous attempt at treating patients with DM1 with an unconjugated antisense oligonucleotide was discontinued due to lack of efficacy. Therefore, there remains a high unmet medical need for new disease modifying therapies.

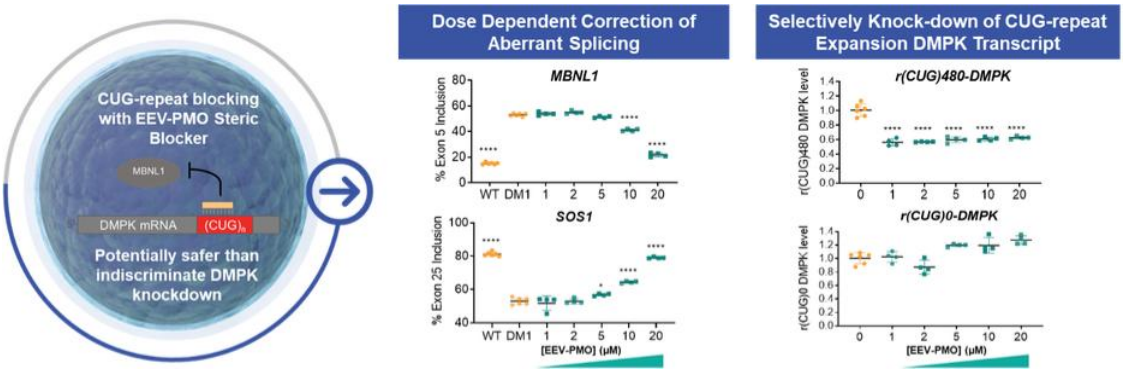
Our Solution

Our approach intends to address the underlying cause of the disease by targeting and blocking the extra CUG triplet repeats occurring in the DMPK mRNA. CAG-repeat antisense oligonucleotides are designed to bind CUG repeat RNA and have been shown to block RNA-protein interactions as well as reduce the level of CUG transcription. We are using a PMO, which we would expect to sterically block CUG repeats and relieve or prevent the sequestration MBNL1 while leaving DMPK mRNA unaffected and leaving healthy levels of DMPK intact.

Summary of Preclinical Data

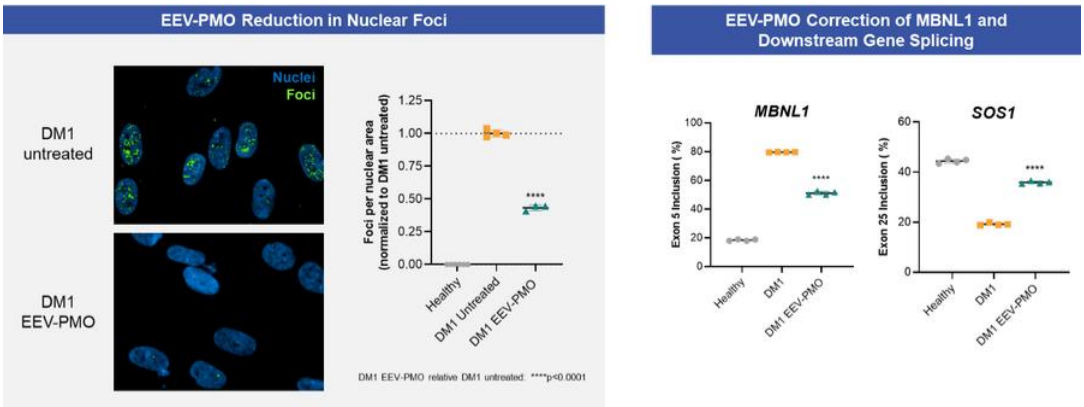
Our initial *in vitro* work was conducted in cell lines engineered to display a very high number of CUG repeats to generate foci, as a model for testing the potential for foci reduction. In our preclinical studies, we observed dose-dependent downregulation of target gene splicing and RNA foci formation in a Hela480 cell line with a high CTG and CUG repeat load and splicing defects knocked in. In a separate *in vitro* experiment, we observed free uptake of CUG-targeting EEV-PMO, EEV-PMO-CAG, (doses from 0-20 mM) resulted in dose dependent splice correction as well as selective and significant knock down of high triplet repeat load (CUG)480 DMPK mRNA transcripts while control (CUG)0 DMPK mRNA transcripts were unaffected.

EEV-PMO-CAG Showed Dose-Dependent Correction of RNA Splicing and Selectively Knocked Down CUG-repeat Containing DMPK Transcript in a HeLa480 Cell Line



Following success in the knock-in model we then assessed the performance of EEV-PMO-CAG in patient derived cell lines.

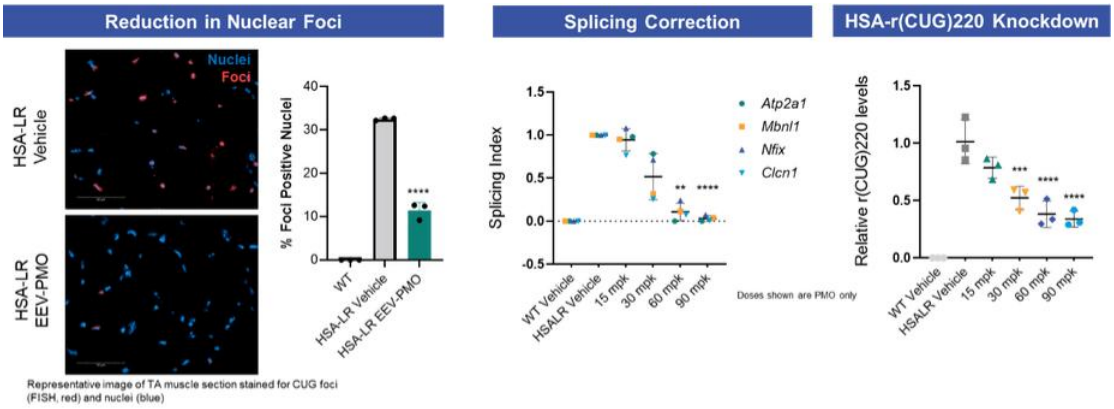
EEV-PMO-CAG Treatment in a DM1 Patient-Derived Cell Line Resulted in Significant RNA Foci Reduction and Dose-Dependent Changes in MBNL1 and Downstream Gene Splicing



In the above experiment immortalized DM1 patient-derived (2,600 CUG repeats) muscle cell line were treated with EEV-PMO and analyzed for correction of aberrant splicing and foci quantification. Administration of EEV-PMO-CAG resulted in a significant dose dependent decrease in MBNL1 exon 5 inclusion. Corrections of other downstream mis-splicings including SOS1 were also observed. Following successful correction *in vitro* we dosed a DM1 murine model with EEV-PMO-CAG.

The human skeletal actin — long repeat (HSA-LR) transgenic mouse contains long CUG repeats has a myotonia phenotype and DM1-relevant splicing defects. As such, this is one of the standard and most frequent mouse models used to assess the potential of a preclinical candidate for DM1. In the experiment below HSA-LR mice were dosed once with vehicle or 15, 30, 60 or 90 mg/kg of EEV-PMO-CAG via IV injections. Healthy wildtype animals were used as controls.

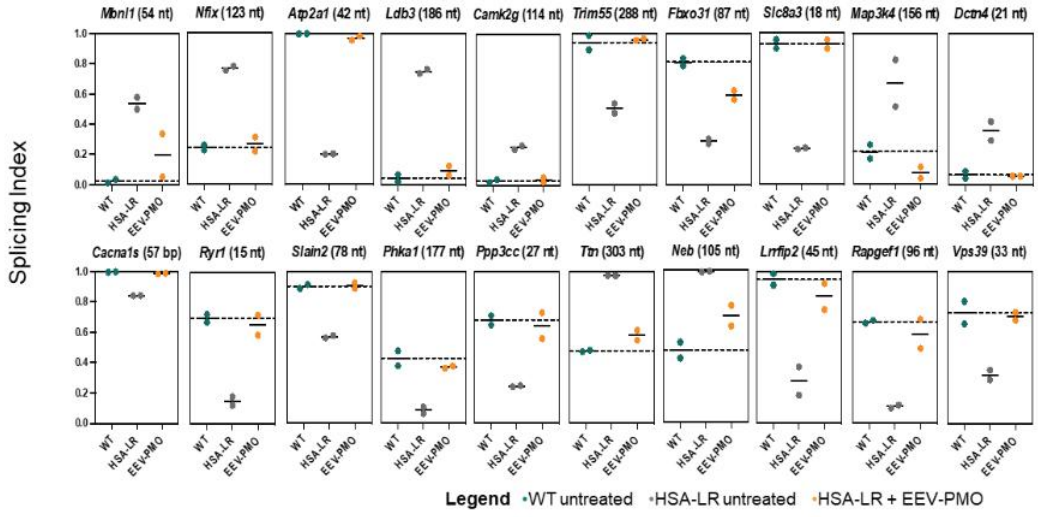
EEV-PMO-CAG Treatment Corrected Aberrant Splicing, Knocked Down CUG-repeat Expansion Transcript And Reduced Nuclear Foci In HSA-LR mice



In this model, EEV-PMO-CAG corrected DM1 relevant splicing defects (Atp2a1 exon 22, Nfix exon 7, Clcn1 exon 7a, Mbnl1 exon 5) at 1-week post injection in the quadriceps, gastrocnemius, triceps and tibialis anterior in a dose dependent manner with higher doses approaching or equivalent to those observed in the control wild type mice. Similarly, we observed approximately 50% human skeletal actin RNA knockdown in HSA-LR mice at drug concentrations that achieved near complete splicing correction. Finally, we also observed a reduction of over 60% in the number of nuclei with CUG-foci (stained red in above left panel).

We believe that a steric block of CUG repeats may result in destabilization of HSA mRNA and degradation of a certain percentage of HSA mRNA, allowing for tissue-specific differences. Further *in vivo* experiments focused on dosing EEV-PMO-CAG at 60 mg/kg are depicted below.

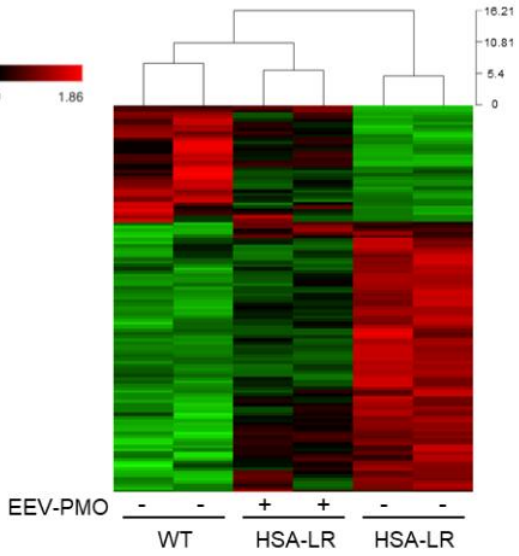
EEV-PMO-CAG Dosed at 60 mg/kg Corrected Multiple MBNL1-responsive Splicing Biomarkers in HSA-LR Mice



In the above experiment HSA-LR mice received a single dose of EEV-PMO-CAG at 60 mg/kg. The choice of MBNL1 dependent biomarkers were selected based on the dynamic range between the wildtype and disease groups as described in medical literature. As noted, EEV-PMO-CAG treatment restored splicing to baseline WT levels, as shown

by the percent spliced in (PSI) values. Going one step further, transcriptomic analysis confirmed normalization at both expression and splicing levels in HSA-LR mice, as illustrated below.

Normalized Global Transcriptome Following a Single IV Injection of EEV-PMO-CAG at 60 mg/kg



In the experiment above HSA-LR mice were dosed with 60 mg/kg EEV-PMO-CAG via IV injection. Gastronemius muscles were assessed on Day 7 via RNA-seq analysis (956 differentially expressed genes; adj. $p<0.05$). Treatment with EEV-PMO-CAG (HSA-LR (+,+) above) resulted in global gene expression correction, shifting away from a disease profile (in red, HSA-LR (-,-) above) and toward that of wild type mice (in green, WT above).

In summary, we observed that EEV-PMO-CAG treatment across a variety of models resulted in highly specific, significant and durable splice correction, and a substantial shift in the transcriptome. Collectively, these experiments suggest the potential for improved functional outcomes. We believe that a steric blocker of CUG repeats that leaves healthy levels of DMPK intact has the potential to be both efficacious and safer than less discriminate approaches.

Clinical Development Plan

Following regulatory feedback and potential authorization to proceed from the FDA based on our IND submission, which we would expect to seek in 2023, we plan to initiate ascending dose studies of EEV-PMO-CAG to assess safety and tolerability and evaluate PKs, mRNA knockdown and spliceopathy in adult patients with DM1. We also plan to explore various measures of clinical activity and quality of life metrics.

Additional Preclinical Programs

Neuromuscular Diseases

Pompe Disease

Pompe disease is a rare, autosomal recessive lysosomal storage disease caused by a mutation in the gene that encodes for glucosidase alpha acid (GAA), which results in an absence or deficiency of GAA protein. Normally, the body uses GAA to break down the complex carbohydrate glycogen and convert it into glucose. Failure to achieve proper breakdown and abnormalities in glycogen metabolism result in the excessive accumulation of glycogen in the body's cells, particularly in cardiac, smooth, and skeletal muscle cells, which can lead to impairment and degradation of normal tissue and organ function. Patients with Pompe disease experience serious muscle-related problems, including

progressive muscle weakness throughout the body, especially in the legs, trunk and diaphragm. As the disorder progresses, breathing problems can lead to respiratory failure.

To date, more than 300 pathogenic mutations have been identified in GAA. Pompe disease is commonly estimated to affect between 5,000 and 10,000 patients in the aggregate in the United States and Europe; however, the advent of newborn screening suggests the disease is underdiagnosed.

Based on the age of onset and severity of symptoms, Pompe disease is typically classified as either infantile-onset Pompe disease (IOPD) or late-onset Pompe disease (LOPD). IOPD is characterized by severe muscle weakness and abnormally diminished muscle tone and usually manifests within the first few months of life. If left untreated, IOPD is often fatal due to progressive cardiac failure, respiratory distress or malnutrition resulting from feeding difficulties. LOPD presents in childhood, adolescence or adulthood. Patients with LOPD typically have milder symptoms, such as reduced mobility and respiratory problems. Patients with LOPD experience progressive difficulty walking and respiratory decline. Initial symptoms of LOPD may be subtle and go unrecognized for years.

Current Treatment Landscape and Limitations

The only currently approved therapies for Pompe disease are alglucosidase alfa (Lumizyme in the United States, Myozyme in other geographies) and avalglucosidase alfa-ngpt (Nexviazyme in the United States), which are both forms of ERT delivered via IV infusions. Although infantile patients treated with ERT for Pompe disease have demonstrated improved survival, ERT is not curative, and many patients in long-term observational studies continue to have increased risk of both cardiomyopathy and heart failure. These patients also experience residual muscle weakness, including difficulties swallowing and the attendant increased risk of aspiration. ERT is particularly limited in its ability to improve skeletal muscle myopathy and respiratory dysfunction, primarily due to its inability to penetrate key tissues affected by the disease, a lack of activity in the cytosol and potential immunogenicity. Despite the availability of ERT, there remains significant unmet medical need in patients with either IOPD or LOPD.

Our Solution

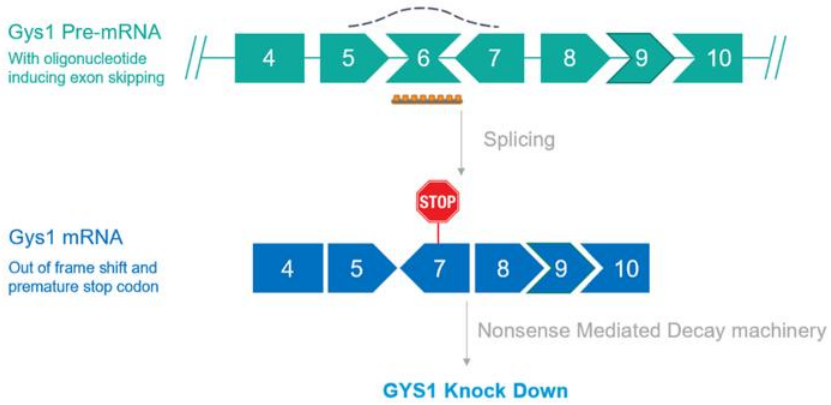
Our Pompe disease program focuses on the development of a potentially disease-modifying treatment, which mitigates the production of glycogen in the cytosol of the cell. Leveraging the modularity of our EEV Platform, we are utilizing EEV-PMOs that target the mRNA that encodes glycogen synthetase 1 (GYS1), a protein required for the synthesis of glycogen in muscle cells. Our EEV-PMO is expected to provide a complementary mechanism of action to GAA replacement, which increases glycogen processing in the lysosome. Together these therapies may improve therapeutic outcomes.

We believe that an EEV-PMO based approach is well suited for the treatment of patients with either IOPD or LOPD because of the ability to specifically inhibit GYS1 in the muscle.

Summary of Preclinical Data

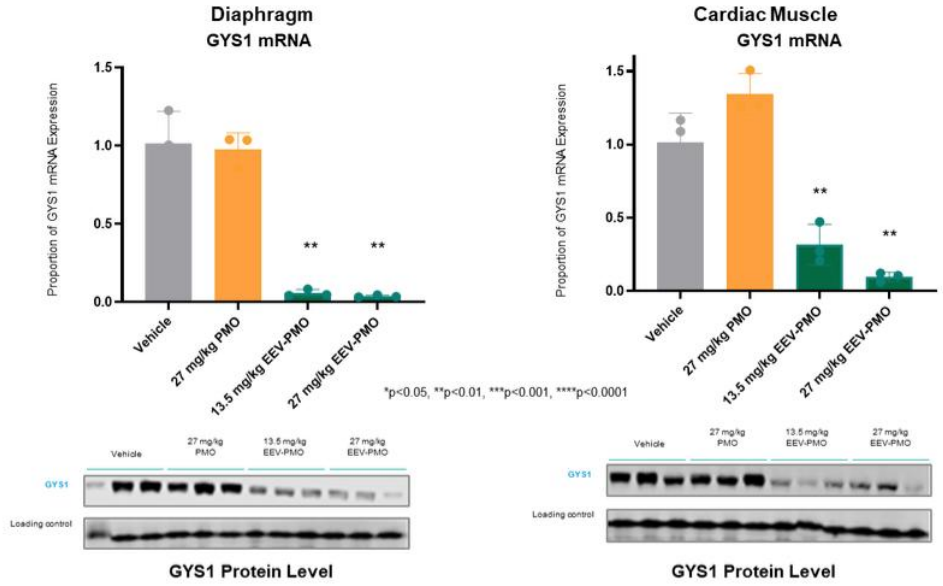
Our therapeutic strategy involves EEV-PMO induced exon skipping, which is similar to our DMD strategy. We believe the more advanced DMD programs lay the foundation for the potential clinical success of our Pompe disease program. The approach in Pompe disease involves knockdown of GYS1 expression by inducing exon skipping to shift the reading frame and induce the reading of a premature stop codon, as illustrated below, resulting in subsequent nonsense-mediated mRNA decay (NMD). NMD prevents the translation of protein production.

GYS1 Knockdown Via Exon Skipping, To Drive Premature Stop Codon Presentation And mRNA Decay



GYS1/GAA double knockout mice, when compared to the GAA single knockout mice, have exhibited a profound reduction in the amount of glycogen in the heart and skeletal muscles, a significant decrease in lysosomal swelling and autophagic build-up. These cellular-level changes lead to cardiomegaly correction, normalization of glucose metabolism and correction of muscle atrophy. We believe, and medical literature suggests, that, despite the absence of GAA, the elimination of GYS1 plays an important role in glycogen metabolism. Furthermore, this mouse model allows us to test the more general utility of NMD and the more specific goal of GYS1 knockdown by an EEV-PMO *in vivo*.

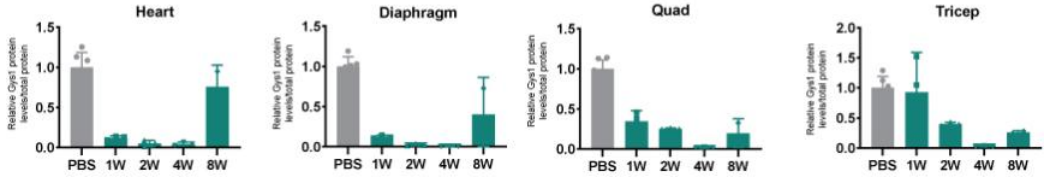
Dose-Dependent EEV-PMO Knockdown of GYS1 Gene Expression and Protein Production in Skeletal and Cardiac Muscles Versus PMO Alone



In the experiment above, GAA knockout mice (GAA-/-) were injected with a single IV dose of either 13.5 mg/kg of EEV-PMO, 27 mg/kg of EEV-PMO, 27 mg/kg of PMO or a negative control (vehicle). GYS1 mRNA and

protein levels were measured one-week post-injection and a significant knockdown of both was observed in both the EEV-PMO arms, but not in the unconjugated PMO arm. This pharmacodynamic result is notable given that this is a single dose experiment administered at very low doses, and it suggests that GYS1 is an addressable target. We further demonstrated that these protein level reductions were durable up to eight weeks post IV dose of 13.5 mg/kg EEV-PMO.

Durable EEV-PMO Knockdown of GYS1 Protein Production in Skeletal and Cardiac Muscles



We believe this result demonstrates the potential of using exon skipping to drive NMD, which potentially opens a broad range of therapeutic indications where a downregulation of gene expression is needed.

Development considerations for GYS1 (Pompe disease and beyond)

We plan to continue studying Pompe disease and select our first Pompe EEV-PMO therapeutic candidate for patients with LOPD by the end of 2023. Although ERT is an effective treatment for some patients, many will fail to adequately respond, or appear to lose response over time. Pending completion of IND-enabling studies, submission of an IND and obtaining regulatory feedback, we expect to initiate trials in combination with ERT to assess safety, tolerability and PK in patients with LOPD. Additionally, we plan to initiate clinical trials involving pediatric patients with IOPD.

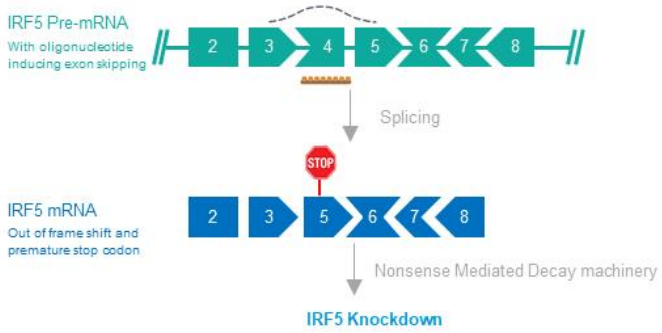
Beyond Pompe disease, we continue to explore a number of additional diseases where GYS1 knockdown is relevant. In addition, we continue to assess other neuromuscular diseases such as FSHD.

Immunology / Oligonucleotides

Interferon Regulatory Factors (IRFs) are a family of transcription factors that regulate transcription of interferons, which are associated with both innate and adaptive immunity pathways. IRF5 in particular operates as a master switch in macrophages and is implicated in proinflammatory cytokine release and fibrosis formation across a range of high unmet need diseases, making this an attractive potential “pipeline in a product.” IRF5 polymorphisms related to higher expression have been associated with susceptibility to inflammatory and autoimmune diseases. Increased IRF5 mRNA level is strongly correlated with disease pathology. IRF5 knockout mice have been shown to have reduced inflammatory phenotype and relevant fibrosis in many disease models including non-alcoholic steatohepatitis (NASH), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), rheumatoid arthritis (RA), asthma and neuropathic pain, among many others.

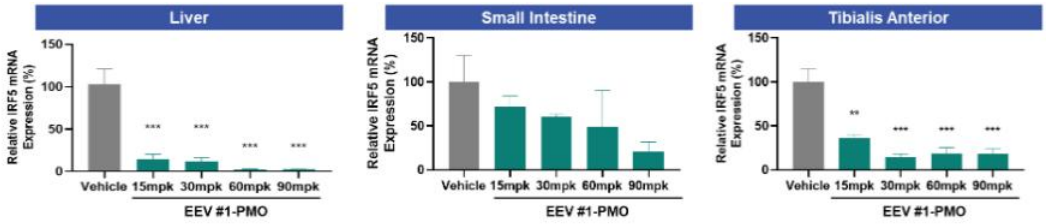
Downregulating IRF5 represents a promising treatment strategy for multiple immune-mediated and inflammatory diseases. We are currently leveraging multiple oligonucleotide strategies for IRF5 downregulation. In preclinical studies, we have demonstrated knockdown of IRF5 protein levels as well as knocking down downstream expression of the pro-inflammatory cytokines.

Downregulation Of IRF5 Via Exon Skipping To Drive Premature Stop Codon Presentation And mRNA Decay



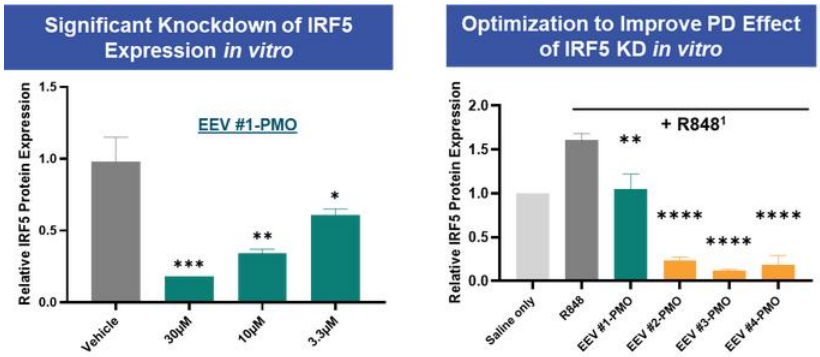
Initial results suggest that EEV-PMO-mediated downregulation of IRF5 mRNA expression in different tissue-resident macrophages has the potential to target multiple disease areas, such as NASH, IBD, SLE and RA.

IRF5 Knockdown In Vivo (WT Model)



In the experiment above, wild type mice were treated with two doses of EEV #1-PMO on Days 0 and 3. Samples were collected on Day 7 for qPCR to measure mRNA levels. In each of the tissues evaluated, a dramatic and dose dependent reduction in relative IRF5 mRNA was observed, as compared with a negative control. Following a screening process, several high potential constructs were tested *in vitro*. We are working to optimize the construct in order to identify a potential clinical candidate.

Optimization of EEV-PMO Targeting IRF5



In the left panel above, mouse macrophage cells treated with the EEV #1-PMO showed a statistically significant reduction of IRF5 protein levels at doses of 30, 10 and 3 uM. In the right panel mouse macrophage cells were pre-treated with 2 μM of EEV-PMOs #1-4 for 4 hours, followed by stimulation with R848, an imidazoquinoline compound that is a specific activator of toll-like receptor (TLR) 7/8, overnight. At 24 hours post treatment, cells were harvested and

evaluated by Western Blot. When compared to the initial EEV #1-PMO which was depicted in the prior *in vivo* model and in the left panel of the *in vitro* data above, we observed a significant improvement in relative potency, as measured by IRF5 protein expression.

We are currently conducting preclinical studies evaluating the delivery of IRF5-targeting EEV- PMOs in disease mouse models with the expectation of *in vivo* proof of concept in 2022 and the potential for candidate selection as early as 2023.

Protein Inhibition and Degradation Therapeutics

When proteins become old, mutated, misfolded or expended, they are degraded by the body through the ubiquitin proteasome system in which cells mark or tag a particular protein for disposal by attaching several molecules of the small regulatory protein ubiquitin.

Several therapeutic approaches are designed to work at the protein level by modulating the ubiquitin proteasome system to harness the cell's natural protein disposal system to degrade and remove a protein. Unlike more traditional signaling inhibitors that need a 1:1 inhibitor-to-target activity ratio, degraders can continuously function and show sub-stoichiometric properties. We believe this means that potentially lower doses and a wider therapeutic index may be possible. This benefit may be enhanced if a higher percentage of the degrader can access the protein in the cell.

Our EEV Platform has the potential to deliver highly selective large molecule protein degraders with activity against disease-causing proteins. Our constructs are designed to induce the ubiquitination and subsequent degradation of proteins in one step, without the need for a separate E3 recruiting moiety or a molecular glue. Furthermore, large molecules are generally more selective than small molecules.

We are exploring biologically validated targets that have been undruggable or have been suboptimally drugged. We have initially focused on β-catenin, a protein which is implicated in both mutagenesis and in immune resistance. This contributes to the carcinogenesis, tumor progression and metastasis of several cancers, including hepatocellular carcinoma, pancreatic, lung, breast, ovarian and colon cancers. We believe a β-catenin degrader may both mitigate tumor progression and (re)sensitize the tumor to immunotherapy. We are currently conducting preclinical studies and have observed both intracellular uptake and downstream signal inhibition. We are expecting *in vivo* proof of concept in 2022 and the potential for candidate selection as early as 2023.

Our Solution

We are currently developing a library of high affinity intracellular antibodies using *in vitro* phage selection of an alpaca immune library and are screening for target engagement, degradation and downstream signal inhibition. We have observed ERK / c-Myc pathway modulation in an HCT116 xenograft colorectal cancer model.

Protein- and Enzyme-Based Therapeutic Candidates

Mitochondrial Neurogastrointestinal Encephalomyopathy (MNGIE): ENTR 501

MNGIE is a slowly progressive, rare autosomal recessive disease caused by mutations in the TYMP gene encoding thymidine phosphorylase (TP). MNGIE is a clinically distinct disorder characterized by extraocular muscle weakness, peripheral neuropathy, progressive gastrointestinal dysmotility, severe cachexia, leukoencephalopathy, and mitochondrial defects including abnormalities of mitochondrial DNA (mtDNA). The disease is highly variable in presentation and relentlessly progressive and fatal, with an average age-at-onset of around 18-years-old and an average age-at-death of 35-years-old. Studies in MNGIE patients have shown that biallelic TYMP mutations cause severe loss of TP activity and dramatic elevation of TP substrates, the pyrimidine nucleosides thymidine (Thd) and deoxyuridine (dUrd) in tissues and plasma. Increased Thd and dUrd leads to deoxynucleoside triphosphate (dNTP) pool imbalance, instability of mtDNA, mitochondrial damage, and, consequently, the resulting MNGIE phenotype.

Our Solution

Our ENTR-501, an intracellular TP ERT, program is in development for the treatment of MNGIE. ENTR-501 has shown robust reduction in the accumulation of thymidine in animal models. Preliminary preclinical studies have also demonstrated that ENTR-501 can reduce toxic TP substrate accumulation below the levels observed in wild-type mice. We believe that ENTR-501 could reduce plasma and tissue levels of toxic TP substrates in patients with MNGIE (both adults and children) to sub-pathogenic levels with the potential to improve clinical symptoms and impact the progression of disease.

We have completed IND-enabling studies for the MNGIE program. In 2020, we made the strategic decision to focus the majority of our immediate efforts on EEV-oligonucleotide opportunities. In order to support ENTR-501 progress, we are exploring partnership opportunities with organizations that have the resources and expertise to continue the development of ENTR-501 into and through clinical development. We continue to believe that the program may have an important role in the future treatment of patients with MNGIE.

Central Nervous System / Oligonucleotides

Neurodegenerative diseases are generally progressive in nature and can result in cognitive decline, functional impairment and eventually death. The rapidly growing patient population represents one of the largest unmet medical needs of our time. We have successfully demonstrated delivery to a wide variety of structures, including the cerebellum, cortex, and hippocampus in the brain, as well as the dorsal root ganglia, the spinal cord, and cells within the nervous system. Importantly, we have observed EEV-PMO concentrations in these tissues up to 60-fold higher when compared with PMO alone. Disease targets we are interested in potentially pursuing include Alzheimer’s disease, glucocerebrosidase administration or GBA gene upregulation for Gaucher’s Disease, glucocerebrosidase administration or GBA gene upregulation for Parkinson’s Disease and CAG trinucleotide repeat modulation for Huntington’s Disease.

Our most advanced CNS focused program is being developed for the treatment of Alzheimer’s disease. The Alzheimer’s Association estimates that in 2021 there are approximately 6.2 million Americans who have Alzheimer’s disease. We are not aware of any inhibitor-based therapies targeting the proteins thought to be the cause of these neurodegenerative diseases that have shown clinical benefits to date and only one, aducanumab, has received an accelerated approval from the FDA on the basis of reducing amyloid beta plaques in the brain. While some existing products provide symptomatic relief to Alzheimer’s patients, they have significant side effect risks and over time gradually lose their effectiveness in treating the symptoms of the disease.

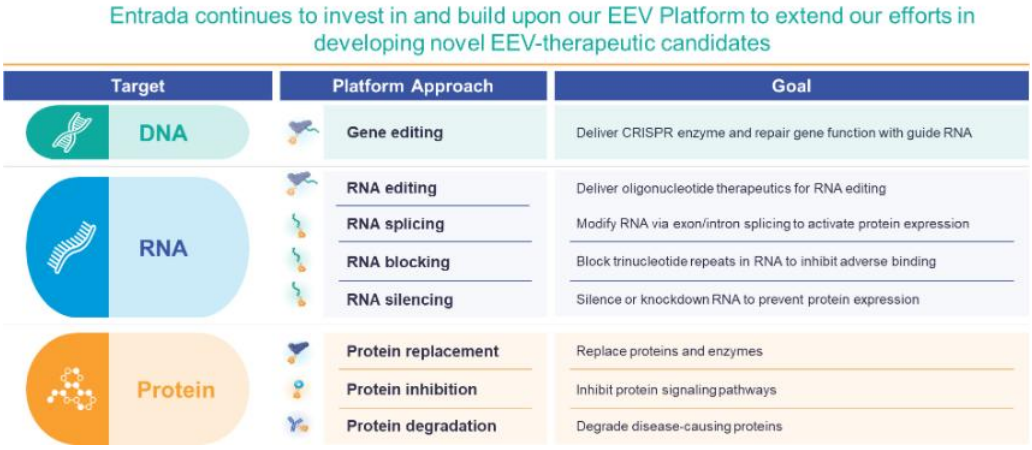
Our Solution

Genome-wide association studies have identified many Alzheimer’s disease risk genes related to immune response and microglia including the phagocytic receptor CD33 and two single nucleotide polymorphisms (rs3826656 and rs3865444) appear to confer increased risk for late onset Alzheimer’s disease and show increased CD33 levels. CD33 otherwise known as siglec-3, is a membrane-bound receptor which regulates innate immune function by limiting the downstream signaling of SHP1 and blocking the inhibition of PI3K. In the CNS, expression is restricted to microglia and macrophages. CD33 mRNA and protein expression is elevated in brains of sporadic Alzheimer’s disease patients and evidence suggests CD33 increases may reduce microglial phagocytosis and inhibit amyloid-beta clearance, potentially driving disease progression. We have employed an exon skipping approach in NHPs to generate an impaired isoform of the CD33 receptor. We believe that our EEV-CD33 may enable activation of otherwise quiescent microglia in the brain to clear amyloid-beta.

Additional Platform Applications

There are a number of additional EEV conjugates that are in discovery. We are leveraging the modularity of the platform to develop opportunities as diverse as EEV-CRISPR-Cas delivery for gene editing, EEV-antibody oligonucleotide conjugates for enhanced tissue tropism and blood brain barrier carriage, as well as novel EEV-ERT

therapies. We continually explore strategic opportunities to develop therapies wherever the EEV Platform provides us with the ability to make a difference for patients with devastating diseases.



Competition

The biotechnology and biopharmaceutical industries generally, and the neuromuscular disease field specifically, are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technology, the expertise of our team, and our development experience and scientific knowledge in the field of muscle diseases, oligonucleotide therapeutics and manufacturing 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. Any therapeutic candidates that we successfully develop and commercialize may compete with existing therapies and new therapies that may become available in the future.

Currently, patients with DMD are treated with corticosteroids to manage the inflammatory component of the disease. EMFLAZA (deflazacort) is an FDA-approved corticosteroid marketed by PTC Therapeutics, Inc. (PTC). In addition, there are four FDA-approved exon skipping drugs: EXONDYS 51 (eteplirsen), VYONDYS 53 (golodirsen), and AMONDYS 45 (casimersen), which are PMOs approved for the treatment of patients with DMD who are amenable to exon 51, exon 53 and exon 45 skipping, respectively, and are marketed by Sarepta Therapeutics, Inc. (Sarepta), and VILTEPSO (vitolarsen), a PMO approved for the treatment of patients with DMD who are amenable to exon 53 skipping, which is marketed by Nippon Shinyaku Co. Ltd. Companies focused on developing treatments for DMD that target dystrophin mechanisms, as does our DMD program, include Sarepta with SRP-5051, a peptide-linked PMO currently being evaluated following a Phase 2 clinical trial for patients amenable to exon 51 skipping along with SRP-5053,SRP-5045 and SRP-5044 in preclinical development, PTC with ataluren, a small molecule targeting nonsense mutations in a Phase 3 clinical trial, Avidity Biosciences, Inc. (Avidity), which is in preclinical development with an antibody oligonucleotide conjugate for exons 44 (AOC-1044), 45 and 51 that targets dystrophin production, Wave Life Sciences Ltd., which is clinically evaluating WVE-N531, a splicing candidate that is designed to target exon 53 within the dystrophin gene, Dyne Therapeutics, Inc. (Dyne), which is pursuing antibody fragment-oligonucleotide conjugates for exons 44, 45, 51 (DYNE-251), and 53, PepGen, Inc. with PGN-EDO51, a preclinical candidate designed to address exon 51, and BioMarin Pharmaceutical Inc., which is in preclinical development with BMN 351, an antisense oligonucleotide therapy for exon 51. In addition, several companies are developing gene therapies to treat DMD, including Audentes Therapeutics, Inc. (AT466 AAV antisense exon 2 skipping candidate, and AT751 and AT753, AAV-antisense exon 51 and 53 skipping candidates, respectively), Pfizer Inc. (PF 06939926), Sarepta (SRP-9001 and Galgt2 gene therapy program), and Solid Biosciences Inc. (SGT-001). Gene editing treatments that are in preclinical development are also being pursued by Vertex Pharmaceuticals, Inc. (Vertex) and Sarepta. We are also aware of several companies targeting non-dystrophin mechanisms for the treatment of DMD.

There are currently no approved therapies to treat the underlying cause of DM1. Therapeutic candidates currently in development to treat DM1 include: tideglusib, a GSK3-ß inhibitor in late-stage clinical development by AMO Pharma Ltd. For the congenital phenotype of DM1; AOC-1001, an antibody linked siRNA in clinical development

by Avidity; DYNE-101, an antibody fragment conjugated to an ASO targeting DM1 protein kinase knockdown in preclinical development by Dyne; a peptide-nucleic acid targeting CUG repeats in development by NeuBase Therapeutics, Inc.; EDOMD1, a linear peptide conjugated to a PMO targeting CUG repeats in preclinical development by PepGen, Inc.; a small molecule targeting GTG repeats in preclinical development by Design Therapeutics, Inc.; gene editing treatments in preclinical development by Vertex; an RNA-targeting gene therapy in preclinical development by Locana, Inc.; and small molecules interacting with RNA in preclinical development by Expansion Therapeutics, Inc.

The only currently-approved therapies for Pompe disease are alglucosidase alfa (Lumizyme in the United States, Myozyme in other geographies) and avalglucosidase alfa-ngpt (Nexviazyme in the United States), which are both forms of ERT delivered via IV infusions. There is one next-generation GAA enzyme in registration from Amicus Therapeutics Inc. (Amicus), and there are four gene therapies in the early stages of clinical development from Astellas Pharma Inc., Bayer AG, Roche Holding AG and Lacerta Therapeutics, Inc. There are five gene therapies in preclinical development from AVROBIO, Inc., Amicus, Provention Bio Inc., Selecta Biosciences, Inc. and Sarepta. There are two preclinical therapies targeting GYS1 inhibition from Maze Therapeutics, Inc. and Avidity, respectively. Denali has an ERT in preclinical development.

Many of our competitors, either independently or with strategic partners, have substantially greater financial, technical and human resources than we do. Accordingly, our competitors may be more successful than we are in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approval for treatments and achieving widespread market acceptance. These companies also compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials and acquiring technologies complementary to, or necessary for, our programs. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

Our commercial potential could be substantially limited if our competitors develop and commercialize products that are more effective, safer, less toxic, more convenient or less expensive than any products we may develop. In geographies that are critical to our commercial success, competitors may also obtain regulatory approvals before us, resulting in our competitors building a strong market position in advance of the entry of our products. In addition, our ability to compete may be affected in many cases by insurers or other third-party payers seeking to encourage the use of other drugs. The key competitive factors affecting the success of any products we may develop are likely to be their efficacy, safety, convenience, price and availability of reimbursement.

Intellectual Property

We strive to protect our proprietary technology, inventions, improvements, platforms, program candidates, therapeutic candidates and components thereof, their methods of use and processes for their manufacture that we believe are important to our business, including by obtaining, maintaining, defending and enforcing patent and other intellectual property rights for the foregoing in the United States and in foreign jurisdictions. We also rely on trade secrets and confidentiality agreements to protect our confidential information and know-how and other aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

Our future commercial success depends in part on our ability to:

- obtain, maintain, enforce and defend patent and other intellectual property rights for our important technology, inventions and know-how; preserve the confidentiality of our trade secrets and other confidential information;
- obtain and maintain licenses to use and exploit intellectual property owned or controlled by third parties;
- operate without infringing, misappropriating or otherwise violating any valid and enforceable patents and other intellectual property rights of third parties; and
- defend against challenges and assertions by third parties challenging the validity or enforceability of our intellectual property rights, or our rights in our intellectual property, or asserting that the operation of our business infringes, misappropriates or otherwise violates their intellectual property rights.

Our portfolio consists of owned and exclusively licensed patents and applications. As of February 28, 2022, there are 38 distinct patent families (21 families with non-provisional applications and 17 families with pending provisional applications) covering compositions of matter, manufacturing and uses related to our business. Among these patent families, we have 75 pending applications (including PCT, provisional and non-provisional applications) in the U.S., European Patent Convention, China, Canada, Hong Kong, Japan, and Taiwan; and 61 granted patents in the U.S., European Patent Convention, India, Japan, and Hong Kong (including a total of 45 member state validations of three European patents). Of these pending applications and granted patents, the licensed patent applications are pending in U.S., European Patent Convention, China, Canada, Hong Kong, Japan, and Taiwan; and licensed patents are granted in the U.S., European Patent Convention, China, India, Japan, and Hong Kong.

Our owned and licensed patent estate covers various aspects of our programs and technology, including various embodiments of our EEV Platform; proprietary enzyme, peptide, oligonucleotide and CRISPR conjugates; methods of treatment; and aspects of manufacturing. The portfolio includes patents covering certain embodiments of the EEV Platform that don't relate to our lead therapeutic candidates with granted patents in the U.S. (3), India, Japan, China, Hong Kong and Europe (including 37 European validation states). The extent to which any patents, if and when granted, will cover our therapeutic candidates is uncertain. Any U.S. or foreign patents issued from national stage filings of our PCT patent applications and any U.S. patents issued from non-provisional applications we have filed or may file in connection with our provisional patent applications would be scheduled to expire on various dates from 2036 through 2042, without taking into account any possible patent term adjustments or extensions and assuming payment of all appropriate maintenance, renewal, annuity and other governmental fees.

Patent Prosecution

A PCT patent application is not eligible to become an issued patent until, among other things, we file one or more national stage patent applications in the jurisdictions in which we seek patent protection and do so within prescribed timelines of the PCT patent application's priority date. These prescribed timelines are generally 30 months, 31 months or 32 months, depending on the jurisdiction. If we do not timely file any national stage patent applications, we may lose our priority date and any potential patent protection on the inventions disclosed in such PCT patent application.

Moreover, a provisional patent application is not eligible to become an issued patent. A provisional patent application may serve as a priority filing for a non-provisional patent application we file within 12 months of such provisional patent application. If we do not timely file non-provisional patent applications, we may lose our priority date with respect to our existing provisional patent applications and any potential patent protection on the inventions disclosed in our provisional patent applications.

While we intend to timely file additional provisional patent applications, as well as national stage and non-provisional patent applications relating to our provisional applications or PCT patent applications, we cannot predict whether any of our patent applications will result in the issuance of patents. If we do not successfully obtain patent protection, or if the scope of the patent protection we or our licensors obtain with respect to our therapeutic candidates or technology is insufficient, we will be unable to use patent protection to prevent others from using our technology or from developing or commercializing technology and products similar or identical to ours or other similar competing products and technologies. Our ability to stop third parties from making, using, selling, offering to sell, importing or otherwise commercializing any of our technology, inventions and improvements, either directly or indirectly, will depend in part on our success in obtaining, maintaining, defending and enforcing patent claims that cover our technology, inventions and improvements.

The patent positions of companies like ours are generally uncertain and involve complex legal and factual questions. The protection afforded by a patent varies on a product-by-product basis, from jurisdiction-to-jurisdiction, and depends upon many factors, including the type of patent, the scope of its coverage, the availability of patent term adjustments and regulatory-related patent term extensions, the availability of legal remedies in a particular jurisdiction, and the validity and enforceability of the patent. Patent laws and related enforcement in various jurisdictions outside of the United States are uncertain and may not protect our rights to the same extent as the laws of the United States. Changes in the patent laws and rules, whether by legislation, judicial decisions or regulatory interpretation, in the United States and other jurisdictions may have uncertain affects that could improve or diminish our ability to protect our inventions and obtain, maintain, defend and enforce our patent rights, and could therefore affect the value of our business in uncertain ways.

The area of patent and other intellectual property rights in biotechnology is evolving and has many risks and uncertainties, and third parties may have blocking patents and other intellectual property that could be used to prevent us from commercializing our platform and therapeutic candidates and practicing our proprietary technology. Our patent rights may be challenged, narrowed, circumvented, invalidated or ruled unenforceable, which could limit our ability to stop third parties from marketing and commercializing related platforms or therapeutic candidates or limit the term of patents that cover our platform and any therapeutic candidates. In addition, the rights granted under any issued patents may not provide us with protection or competitive advantages against third parties with similar technology, and third parties may independently develop similar technologies.

Moreover, because of the extensive time required for development, testing and regulatory review of a potential product, it is possible that before any of our therapeutic candidates can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby reducing any competitive advantage provided by the patent. For this and other risks related to our proprietary technology, inventions, improvements, platforms and therapeutic candidates and intellectual property rights related to the foregoing, please see the section entitled "Risk Factors—Risks Related to Our Intellectual Property."

Patent Term

The term of individual patents depends upon the laws of the jurisdictions in which they are obtained. In most jurisdictions in which we file, the patent term is 20 years from the filing date of a PCT patent application or, if a PCT application is not filed, the earliest date of filing of the first non-provisional patent application to which the patent claims priority. However, the term of U.S. patents may be extended or adjusted for delays incurred due to compliance with FDA requirements or by delays encountered during prosecution that are caused by the United States Patent and Trademark Office (USPTO). For example, in the United States, a patent claiming a new chemical entity or biologic product, its method of use or its method of manufacture may be eligible for a limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Act) for up to five years beyond the normal expiration date of the patent. Patent term extension cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date in the United States. Only one patent applicable to an approved product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent for which extension is sought and within 60 days of FDA approval of the product. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. During the period of extension, if granted, the scope of exclusivity is limited to the approved product for approved uses. Some foreign jurisdictions, including Europe and Japan, have analogous patent term extension provisions, which allow for extension of the term of a patent that covers a drug approved by the applicable foreign regulatory agency. For more information on patent term extensions, see "Business—Government Regulation—Patent Term Restoration and Extension and Marketing Exclusivity." In the future, if and when any therapeutic candidates we may develop receive FDA approval, we expect to apply for patent term extensions on issued patents covering those therapeutic candidates. Moreover, we intend to seek patent term adjustments and extensions for any of our issued patents in any jurisdiction where such adjustments and extensions are available. However, there is no guarantee that the applicable authorities, including the USPTO and the FDA, will agree with our assessment of whether such adjustments and extensions should be granted, and even if granted, the length of such adjustments and extensions.

Trade Secrets

In addition to patent protection, we also rely on trade secrets, know-how, unpatented technology and other proprietary information to strengthen our competitive position. We currently, and may continue in the future continue to, rely on third parties to assist us in developing and manufacturing our products. Accordingly, we must, at times, share trade secrets, know-how, unpatented technology and other proprietary information, including those related to our platform, with them. We may in the future also enter into research and development collaborations with third parties that may require us to share trade secrets, know-how, unpatented technology and other proprietary information under the terms of research and development partnerships or similar agreements. Nonetheless, we take steps to protect and preserve our trade secrets and other confidential and proprietary information and prevent the unauthorized disclosure of the foregoing, including by entering into non-disclosure and invention assignment agreements with parties who have access to our trade secrets or other confidential and proprietary information, such as employees, consultants, outside scientific collaborators, contract research and manufacturing organizations, sponsored researchers and other advisors, at the commencement of their employment, consulting or other relationships with us. In addition, we take other appropriate precautions, such as maintaining physical security of our premises and physical and electronic security of our

information technology systems, to guard against any misappropriation or unauthorized disclosure of our trade secrets and other confidential and proprietary information by third parties.

Despite these efforts, third parties may independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or other confidential or proprietary information. In addition, we cannot provide any assurances that all of the foregoing non-disclosure and invention assignment agreements have been duly executed, and any of the counterparties to such agreements may breach them and disclose our trade secrets and other confidential and proprietary information. Although we have confidence in the measures we take to protect and preserve our trade secrets and other confidential and proprietary information, they may be inadequate, our agreements or security measures may be breached, and we may not have adequate remedies for such breaches. Moreover, to the extent that our employees, contractors, consultants, collaborators and advisors use intellectual property owned by others in their work for us, disputes may arise as to our rights in any know-how or inventions arising out of such work. For more information, please see the section entitled “Risk Factors—Risks Related to Our Intellectual Property.”

License Agreement with The Ohio State University

On May 12, 2017, we entered into an option agreement with Ohio State Innovation Foundation (OSIF), an affiliate of The Ohio State University (OSU) responsible for the commercialization of technology developed at or created by or for OSU, in which the Company obtained an option (OSIF Option Agreement) to license all patents and patent applications involving technologies using cell-penetrating peptides arising out of or related to specified invention disclosures or through a sponsored research agreement executed with OSU on the same date (OSU SRA). On September 26, 2018, we exercised our option pursuant to the terms of the OSIF Option Agreement, and on December 14, 2018, we entered into a license agreement (OSIF License Agreement) for an exclusive, worldwide, sublicensable license under these patents and patent rights, and a non-exclusive, worldwide, sublicensable license under certain related know-how, to develop, commercialize or otherwise exploit products based on these cell-penetrating technologies for the treatment, prevention and diagnosis of any and all diseases or conditions. In addition, the OSIF License Agreement grants a worldwide, perpetual, irrevocable, fully-paid, royalty-free, sublicensable, exclusive license to any rights held by OSIF, OSU or its affiliates covering specifically identified cell-penetrating platform technology.

The term of the OSIF License Agreement will continue until the later of (a) the expiration of the last to expire of the exclusively licensed patent rights, or (b) the end of our obligation to pay royalties under the OSIF License Agreement. Such obligation ends, on a licensed product-by-licensed product and country-by-country basis, on the later of (1) expiration of the last to expire of the valid claims of the exclusively licensed patent rights covering such licensed product in such country, or (2) ten (10) years after the first commercial sale of such licensed product in such country. The last to expire exclusively licensed patent rights and valid claim of such exclusively licensed patent rights are estimated to expire by 2042, excluding any patent term adjustments or extensions. Upon expiration of the OSIF License Agreement at the end of the royalty term, the Company will maintain all license rights as a perpetual and fully paid-up license. Both parties have the right to terminate under certain enumerated circumstances. At our option, we may terminate the OSIF License Agreement for any reason with ninety days’ (90) written notice, or if OSIF is in material breach, after providing thirty (30) days’ notice of termination. OSIF may terminate the agreement at its option immediately upon delivery of written notice if any specified events occur, including failure by the Company to make payments due under the agreement and if the Company is in material breach, in each case pursuant to specified cure periods.

We have typical diligence obligations under the OSIF License Agreement, including the obligation to use commercially reasonable efforts to develop and commercialize at least one licensed product. We may also be obligated to pay aggregate milestone payments of up to $7,950,000, tiered royalties on sales at low single digit percentages, a license maintenance fee of $25,000 per year beginning in 2021 and continuing until the first year in which commercial sales of a licensed product pursuant to the agreement commence. After such commercialization, we are required to make minimum annual payments of $125,000. In addition, in the event of a sublicense, under certain circumstances we may be required to pay up to 15% of non-royalty sublicensing consideration.

Commercialization

Excluding ENTR-501, we intend to retain significant development and commercial rights to our potential therapeutic candidates and, if marketing approval is obtained, to commercialize our therapeutic candidates on our own, or potentially with a partner, in the United States and other regions. We currently have no sales, marketing, or

commercial product distribution capabilities. We intend to build the necessary infrastructure and capabilities over time for the United States, and potentially other regions, following further advancement of our therapeutic candidates. We believe that such a focused sales and marketing organization will be able to address the key specialists in treating the patient populations for which our therapeutic candidates are being developed. Clinical data, the size of the addressable patient population, and the size of the commercial infrastructure and manufacturing needs may all influence or alter our commercialization plans. The responsibilities of the marketing organization would include developing educational initiatives with respect to approved products and establishing relationships with researchers and practitioners in relevant fields of medicine.

Manufacturing

We do not own or operate manufacturing facilities. We currently rely on third-party contract manufacturing organizations (CMOs), and suppliers for EEVs, linkers and nucleotides that comprise ENTR-601-44, EEV-PMO-CAG and our potential therapeutic candidates and the conjugation of these components, and we expect to continue to do so to support our IND-enabling studies and our clinical trials and commercial activities; however, we may seek to establish our own manufacturing facility for IND-enabling studies, clinical studies and long-term commercial supply. As we scale manufacturing, we intend to continue to expand and strengthen our network of CMOs. We believe there are multiple sources for all of the materials required for the manufacture of our therapeutic candidates, as well as multiple CMOs who could assemble the aforementioned components that comprise ENTR-601-44 and our potential therapeutic candidates.

Manufacturing is subject to extensive regulations that impose procedural and documentation requirements. These regulations govern record keeping, manufacturing processes and controls, personnel, quality control and quality assurance. Our CMOs are required to comply with these regulations and are assessed through regular monitoring and formal audits. Our third-party manufacturers are required to manufacture any therapeutic candidates we develop under current Good Manufacturing Practice (cGMP), requirements and other applicable laws and regulations.

We have personnel with extensive technical, manufacturing, analytical and quality experience to oversee all contracted manufacturing and testing activities.

Government Regulation

Government authorities in the United States, at the federal, state and local level and in other countries and jurisdictions, including the European Union, extensively regulate, among other things, the research, development, testing, manufacture, pricing, reimbursement, sales, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting and import and export of drugs and biological products such as those we are developing. The processes for obtaining marketing approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

Licensure and Regulation of Drugs and Biologics in the United States

In the United States, where we are initially focusing our product development, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act (FDCA), and biologics under the FDCA and the Public Health Service Act (PHSA), and their implementing regulations. Both drugs and biologics are also subject to other federal, state and local statutes and regulations. Our therapeutic candidates are early-stage and have not been approved by the FDA for marketing in the United States. Based on our novel therapeutic approach and the broad potential applicability of our EEV Platform to deliver a variety of therapeutic modalities into cells, we are developing therapeutic candidates that would be regulated under the FDCA, and/or the PHSA, and their implementing regulations, as drugs or biologics, depending on the modality of each product candidate. The failure to comply with the applicable U.S. requirements at any time during the product development process, including preclinical testing, clinical testing, the approval process, or post-approval process, may subject an applicant to delays in the conduct of the study, regulatory review and approval and/or administrative or judicial sanctions. These sanctions may include, but are not limited to, the FDA’s refusal to allow an applicant to proceed with clinical testing, refusal to approve pending applications, license suspension, or revocation, withdrawal of an approval, warning letters, adverse publicity, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines and civil or criminal investigations and penalties brought by the FDA or the Department of Justice (DOJ), and other governmental entities, including state agencies.

An applicant seeking approval to market and distribute a new drug or biologic in the United States generally must satisfactorily complete each of the following steps: preclinical laboratory tests, animal studies and formulation studies all performed in accordance with the FDA's Good Laboratory Practices (GLP) regulations, as applicable; completion of the manufacture, under current Good Manufacturing Practices (cGMP) conditions, of the drug substance and drug product that the sponsor intends to use in human clinical trials along with required analytical and stability testing; 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; approval by an independent institutional review board (IRB), representing each clinical trial site before each clinical trial site may be initiated; performance of adequate and well-controlled human clinical trials, in accordance with current Good Clinical Practices (GCP), and any additional nonclinical studies required to establish the safety, efficacy, potency and purity of the product candidate for each proposed indication; preparation and submission to the FDA of a new drug application (NDA), or a Biologics License Application (BLA), for a biologic product, requesting marketing for one or more proposed indications, including submission of detailed information on the manufacture and composition of the product in clinical development and proposed labelling; review of the product by an FDA advisory committee, where appropriate or if applicable; satisfactory completion of one or more FDA inspections of the manufacturing facility or facilities, including those of third parties, at which the product, or components thereof, are produced to assess compliance with cGMP and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity; satisfactory completion of any FDA audits of the preclinical studies and clinical trial sites to assure compliance with GLP, as applicable, and GCP, and the integrity of clinical data in support of the NDA or BLA; payment of user fees under the Prescription Drug User Fee Act (PDUFA); securing FDA approval of the NDA or BLA; and compliance with any post-approval requirements, including the potential requirement to implement a Risk Evaluation and Mitigation Strategy (REMS), and any post-approval studies or other post-marketing commitments required by the FDA.

Preclinical Studies and Investigational New Drug Application

Before testing any therapeutic product candidate in humans, the product candidate must undergo preclinical testing. Preclinical tests include laboratory evaluations of product chemistry, formulation and stability, as well as studies to evaluate the potential for efficacy and toxicity in animal studies. The conduct of the preclinical tests and formulation of the compounds for testing must comply with federal regulations and requirements. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND application.

An IND is an exemption from the FDCA that allows an unapproved product candidate to be shipped in interstate commerce for use in a clinical trial and a request for FDA authorization to administer such investigational product to humans. The IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions about the product or conduct of the proposed clinical trial, including concerns that human research subjects will be exposed to unreasonable health risks. In that case, the IND sponsor and the FDA must resolve any outstanding FDA concerns before the clinical trials can begin or recommence.

As a result, submission of the IND may result in the FDA not allowing the trials to commence or allowing the trial to commence on the terms originally specified by the sponsor in the IND. If the FDA raises concerns or questions either during this initial 30-day period, or at any time during the IND review process, it may choose to impose a partial or complete clinical hold. Clinical holds may be imposed by the FDA when there is concern for patient safety, and may be a result of new data, findings, or developments in clinical, preclinical and/or chemistry, manufacturing and controls or where there is non-compliance with regulatory requirements. This order issued by the FDA would delay either a proposed clinical trial or cause suspension of an ongoing trial, until all outstanding concerns have been adequately addressed and the FDA has notified the company that investigations may proceed. A separate submission to an existing IND must also be made for each successive clinical trial conducted during drug development, and the FDA must grant permission, either explicitly or implicitly by not objecting, before each clinical trial can begin.

Human Clinical Trials in Support of an NDA or BLA

Clinical trials involve the administration of the investigational product candidate to healthy volunteers or patients with the disease or condition to be treated under the supervision of qualified investigators in accordance with GCP requirements. Clinical trials are conducted under protocols detailing, among other things, the objectives of the trial, inclusion and exclusion criteria, the parameters to be used in monitoring safety, and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND.

A sponsor who wishes to conduct a clinical trial outside the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. When a foreign clinical trial is conducted under an IND, all FDA IND requirements must be met unless waived. The FDA will accept a well-designed and well-conducted foreign clinical study not conducted under an IND if the study was conducted in accordance with GCP requirements, and the FDA is able to validate the data through an onsite inspection if deemed necessary. The GCP requirements encompass both ethical and data integrity standards for clinical trials. The FDA's regulations are intended to help ensure the protection of human subjects enrolled in non-IND foreign clinical trials, as well as the quality and integrity of the resulting data. They further help ensure that non-IND foreign trials are conducted in a manner comparable to that required for clinical trials in the United States.

Further, each clinical trial must be reviewed and approved by an IRB either centrally or individually at each institution at which the clinical trial will be conducted. The IRB will consider, among other things, clinical trial design, patient informed consent, ethical factors, the safety of human subjects, and the possible liability of the institution. An IRB must operate in compliance with FDA regulations. The FDA, IRB, or the clinical trial sponsor may suspend or discontinue a clinical trial at any time for various reasons, including a finding that the clinical trial is not being conducted in accordance with GCP requirements or that the participants are being exposed to an unacceptable health risk. Clinical testing also must satisfy extensive GCP rules and the requirements for informed consent.

Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board (DSMB), or data monitoring committee (DMC). This group may recommend continuation of the trial as planned, changes in trial conduct, or cessation of the trial at designated check points based on certain available data from the trial to which only the DSMB/DMC has access. Finally, certain clinical trials involving recombinant or synthetic nucleic acid molecules may be subject to review and approval of an Institutional Biosafety Committee (IBC), in accordance with NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines). An IBC is a local institutional committee that reviews and oversees research utilizing recombinant or synthetic nucleic acid molecules at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment, and such review may result in some delay before initiation of a clinical trial. While the NIH Guidelines are not mandatory unless the research in question is being conducted at or sponsored by institutions receiving NIH funding for recombinant or synthetic nucleic acid molecule research, many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them.

Clinical trials typically are conducted in three sequential phases, but the phases may overlap or be combined. Additional studies may be required after approval.

- Phase 1 clinical trials are initially conducted in a limited population to test the product candidate for safety, including adverse effects, dose tolerance, absorption, metabolism, distribution, excretion and pharmacodynamics in healthy subjects or patients.

- Phase 2 clinical trials are generally conducted in a limited patient population to identify possible adverse effects and safety risks, evaluate the efficacy of the product candidate for specific targeted indications and 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 costly Phase 3 clinical trials.

- Phase 3 clinical trials typically proceed if the Phase 2 clinical trials demonstrate that a dose range of the product candidate is potentially effective and has an acceptable safety profile. Phase 3 clinical trials are generally undertaken within an expanded patient population to further evaluate dosage, provide substantial evidence of clinical efficacy and further test for safety in an expanded and diverse patient population at multiple, geographically dispersed clinical trial sites. A well-controlled, statistically robust Phase 3 trial may be designed to deliver the data that regulatory authorities will use to decide whether or not to approve, and, if approved, how to appropriately label a therapeutic.

In some cases, the FDA may approve an NDA or BLA for a product but require the sponsor to conduct additional clinical trials to further assess the product's safety and effectiveness after approval. Such post-approval trials are typically referred to as Phase 4 clinical trials. These studies are used to gain additional experience from the treatment of patients in the intended therapeutic indication and to document a clinical benefit for products approved under accelerated approval regulations. If the FDA approves a product while a company has ongoing clinical trials that were

not necessary for approval, a company may be able to use the data from these clinical trials to meet all or part of any Phase 4 clinical trial requirement or to request a change in the product labeling. The failure to exercise due diligence with regard to conducting Phase 4 clinical trials could result in withdrawal of approval for products.

Information about applicable clinical trials must be submitted within specific timeframes to the NIH for public dissemination on its ClinicalTrials.gov website.

Under the Pediatric Research Equity Act of 2003, an NDA, BLA or supplement thereto must contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDCA requires that 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 submit an initial Pediatric Study Plan (PSP), within sixty days of an end-of-Phase 2 meeting or as may be agreed between the sponsor and FDA. Those plans must contain an outline of the proposed pediatric study or studies the applicant plans to conduct, including study objectives and design, any deferral or waiver requests, and other information required by regulation. The sponsor and the FDA must reach agreement on the PSP. The FDA or the applicant may request an amendment to the plan at any time.

The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Additional requirements and procedures relating to deferral requests and requests for extension of deferrals are contained in the Food and Drug Administration Safety and Innovation Act. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

Expanded Access to an Investigational Drug for Treatment Use

Expanded access, sometimes called “compassionate use,” is the use of investigational products outside of clinical trials to treat patients with serious or immediately life-threatening diseases or conditions when there are no comparable or satisfactory alternative treatment options. The rules and regulations related to expanded access are intended to improve access to investigational products for patients who may benefit from investigational therapies. FDA regulations allow access to investigational products under an IND by the company or the treating physician for treatment purposes on a case-by-case basis for: individual patients (single-patient IND applications for treatment in emergency settings and non-emergency settings); intermediate-size patient populations; and larger populations for use of the investigational product under a treatment protocol or treatment IND application.

Expanded access may be appropriate when all of the following criteria apply: patient(s) have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition; patient enrollment in a clinical trial is not possible; the potential patient benefit justifies the potential risks of the treatment and the potential risks are not unreasonable in the context or condition to be treated; and the expanded use of the investigational drug for the requested treatment will not interfere with initiation, conduct, or completion of clinical investigations that could support marketing approval of the product or otherwise compromise the potential development of the product. There is no obligation for a sponsor to make its drug products available for expanded access; however, as required by the 21st Century Cures Act (Cures Act), a sponsor must make its policy regarding evaluating and responding to expanded access requests publicly available.

In addition, on May 30, 2018, the Right to Try Act was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational products that have completed a Phase 1 clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a manufacturer to make its investigational products available to eligible patients as a result of the Right to Try Act.

Compliance with cGMP Requirements

Before approving an NDA or BLA, the FDA will typically 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 requirements and adequate to assure consistent production of the product within

required specifications. The PHSA emphasizes the importance of manufacturing controls for products like biologics whose attributes cannot be precisely defined.

Manufacturers and others involved in the manufacture and distribution of products must also register their establishments with the FDA and certain state agencies. Both domestic and foreign manufacturing establishments must register and provide additional information to the FDA upon their initial participation in the manufacturing process. Any product manufactured by or imported from a facility that has not registered, whether foreign or domestic, is deemed misbranded under the FDCA. Establishments may be subject to periodic unannounced inspections by government authorities to ensure compliance with cGMPs and other laws. Noncompliance with such requirements can lead to adverse findings by the FDA during these inspections; in instances of significant or continued noncompliance, such adverse findings can serve as the basis for additional regulatory action by the FDA, including but not limited to warning and "untitled" letters.

Review and Approval of an NDA or BLA

The results of product candidate development, preclinical testing and clinical trials, including negative or ambiguous results as well as positive findings, are submitted to the FDA as part of an NDA or BLA requesting approval to market the product. The NDA or BLA must contain extensive manufacturing information and detailed information on the composition of the product and proposed labeling as well as payment of a user fee. Under federal law, the submission of most NDAs and BLAs are subject to an application user fee. The sponsor of an approved NDA or BLA is also subject to an annual program fee. Certain exceptions and waivers are available for some of these fees, such as an exception from the application fee for products with orphan designation and a waiver for certain small businesses.

The FDA has 60 days after submission of the application to conduct an initial review to determine whether to accept it for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. Once the submission has been accepted for filing, the FDA begins an in-depth review of the application. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has ten months in which to complete its initial review of a standard application and respond to the applicant, and six months for a priority review of the application. The FDA does not always meet its PDUFA goal dates for standard and priority NDAs and BLAs. The review process may be significantly extended by FDA requests for additional information or clarification. The review process and the PDUFA goal date may be extended by three months if the FDA requests or if the applicant otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

The FDA reviews an NDA or BLA to determine, among other things, whether the product is safe and effective and whether the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product's continued safety, quality and purity. On the basis of the FDA's evaluation of the application and accompanying information, including the results of the inspection of the manufacturing facilities and any FDA audits of preclinical and clinical trial sites to assure compliance with GCPs, the FDA may issue an approval letter or a complete response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. If the application is not approved, the FDA will issue a complete response letter, which will contain the conditions that must be met in order to secure final approval of the application, and when possible, will outline recommended actions the sponsor might take to obtain approval of the application. Sponsors that receive a complete response letter have one year to submit to the FDA information that represents a complete response to the issues identified by the FDA. The FDA will then re-review the application, taking into consideration the response. Failure to respond to a complete response letter will serve as a withdrawal of an application. The FDA will not approve an application until issues identified in any complete response letters have been addressed.

The FDA may also refer the application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. In particular, the FDA may refer applications for novel products or products that 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 recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

If the FDA approves a new product, it may limit the approved indication(s) for use of the product. It may also require that contraindications, warnings, or precautions be included in the product labeling. In addition, the FDA may call for post-approval studies, including Phase 4 clinical trials, to further assess the product's efficacy and/or safety after approval. The agency may also require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms, including a REMS program, to help ensure that the benefits of the product outweigh the potential risks. A REMS can include medication guides, communication plans for healthcare professionals and elements to assure safe use (ETASU). ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring and the use of patent registries. The FDA may prevent or limit further marketing of a product based on the results of post-market studies or surveillance programs. After approval, many types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Fast Track, Breakthrough Therapy and Priority Review

The FDA provides programs intended to facilitate and expedite development and review of new products that are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition. These programs are referred to as fast track designation, breakthrough therapy designation, and priority review designation. These designations are not mutually exclusive, and a product candidate may qualify for one or more of these programs. While these programs are intended to expedite product development and approval, they do not alter the standards for FDA approval.

The FDA may designate a product for fast track designation if it is intended, whether alone or in combination with one or more other products, for the treatment of a serious or life-threatening disease or condition, and it demonstrates the potential to address unmet medical needs for such a disease or condition. For products with fast track designation, sponsors may have greater interactions with the FDA, the product is potentially eligible for accelerated approval and priority review, if relevant criteria are met, and the FDA may initiate review of sections of a product with fast track designation application before the application is complete. This rolling review may be available if the FDA determines, after preliminary evaluation of clinical data submitted by the sponsor, that a product with fast track designation may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information and the sponsor must pay applicable user fees. However, the FDA's time period goal for reviewing a fast track application does not begin until the last section of the application is submitted. In addition, the fast track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

A product may be designated as a breakthrough therapy if it is intended, either alone or in combination with one or more other products, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The FDA may take certain actions with respect to breakthrough therapies, including holding meetings with the sponsor throughout the development process; providing timely advice to the product sponsor regarding development and approval; involving senior managers in the review process; assigning a cross-disciplinary lead for the review team; and taking other steps to design the clinical trials in an efficient manner. Breakthrough designation may be rescinded if a product no longer meets the qualifying criteria.

The FDA may designate a product for priority review if it is a product that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness. The FDA determines, on a case-by-case basis, whether the proposed product represents a significant improvement 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 adverse reaction, documented enhancement of patient compliance that may lead to improvement in serious outcomes, and 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. Priority review designation may be rescinded if a product no longer meets the qualifying criteria.

Accelerated Approval Pathway

The FDA may grant accelerated approval to a product for a serious or life-threatening condition that provides meaningful therapeutic advantage to patients over existing treatments based upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. 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. The FDA may also grant accelerated approval for such a condition when the product has an effect on an intermediate clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality (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. The FDA has limited experience with accelerated approvals based on intermediate clinical endpoints but has indicated that such endpoints generally may support accelerated approval where 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 clinical benefit of a product. Products granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

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 product, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the development and approval of products 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 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 product’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, confirm a clinical benefit during post-marketing studies or dissemination of false or misleading promotional materials would allow the FDA to withdraw the product from the market on an expedited basis. In addition, for products being considered for accelerated approval, the FDA generally requires, unless otherwise informed by the agency, that all advertising and promotional materials intended for dissemination or publication within 120 days of marketing approval be submitted to the agency for review during the pre-approval review period.

Orphan Drug Designation

Orphan drug designation in the United States is designed to encourage sponsors to develop products intended for treatment of rare diseases or conditions. In the United States, a rare disease or condition is statutorily defined as a condition that affects fewer than 200,000 individuals in the United States or that affects 200,000 or more individuals in the United States and for which there is no reasonable expectation that the cost of developing and making available the biologic for the disease or condition will be recovered from sales of the product in the United States.

Orphan drug designation qualifies a company for tax credits and market exclusivity for seven years following the date of the product’s marketing approval if granted by the FDA. An application for designation as an orphan product can be made any time prior to the filing of an application for approval to market the product. After the FDA grants orphan designation, the product must then go through the review and approval process like any other product.

A sponsor may request orphan drug designation of a previously unapproved product or new orphan indication for an already marketed product. In addition, a sponsor of a product that is otherwise the same product as an already approved orphan drug may seek and obtain orphan drug designation for the subsequent product for the same rare disease or condition if it can present a plausible hypothesis that its product may be clinically superior to the first drug. More than one sponsor may receive orphan drug designation for the same product for the same rare disease or condition, but each sponsor seeking orphan drug designation must file a complete request for designation.

If a product with orphan designation receives the first FDA approval for the disease or condition for which it has such designation or for a select indication or use within the rare disease or condition for which it was designated, the product generally will receive orphan drug exclusivity. Orphan drug exclusivity means that the FDA may not approve

another sponsor's marketing application for the same product for the same indication for seven years, except in certain limited circumstances. If a product designated as an orphan drug ultimately receives marketing approval for an indication broader than what was designated in its orphan drug application, it may not be entitled to exclusivity.

The period of exclusivity begins on the date that the marketing application is approved by the FDA and applies only to the indication for which the product has been designated. The FDA may approve a second application for the same product for a different use or a second application for a clinically superior version of the product for the same use. The FDA cannot, however, approve the same product made by another manufacturer for the same indication during the market exclusivity period unless it has the consent of the sponsor, or the sponsor is unable to provide sufficient quantities.

Pediatric Exclusivity

Pediatric exclusivity is another type of non-patent marketing exclusivity in the United States and, if granted, provides for the attachment of an additional six months of marketing protection to the term of any existing regulatory exclusivity, including orphan exclusivity. This six-month exclusivity may be granted if an NDA or BLA sponsor submits pediatric data that fairly respond to a written request from the FDA for such data. 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 that cover the product are extended by six months.

U.S. Patent Term Restoration and Extension and Marketing Exclusivity

In the United States, a patent claiming a new biologic product, its method of use or its method of manufacture may be eligible for a limited patent term extension under the Hatch-Waxman Act, which permits a patent extension of up to five years for patent term lost during product development and FDA regulatory review. Assuming grant of the patent for which the extension is sought, the restoration period for a patent covering a product is typically one-half the time between the effective date of the IND and the submission date of the NDA or BLA, plus the time between the submission date of the NDA or BLA and the ultimate approval date, except that the review period is reduced by any time during which the applicant failed to exercise due diligence. Patent term restoration cannot be used to extend the remaining term of a patent past a total of 14 years from the product's approval date in the United States. Only one patent applicable to an approved product is eligible for the extension, and the application for the extension must be submitted prior to the expiration of the patent for which extension is sought. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. The USPTO reviews and approves the application for any patent term extension in consultation with the FDA.

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

Biosimilars and Exclusivity

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010 (collectively, the ACA), which was signed into law in March 2010, included a subtitle called the Biologics Price Competition and Innovation Act of 2009 (BPCIA). The BPCIA established a regulatory scheme authorizing the FDA to approve biosimilars and interchangeable biosimilars. A biosimilar is a biological product that is highly similar to an existing FDA-licensed "reference product." The FDA has issued multiple guidance documents outlining an approach to review and approval of biosimilars. Under the BPCIA, a manufacturer may submit an application for licensure of a biologic product that is "biosimilar to" or "interchangeable with" a previously approved biological product or "reference product." In order for the FDA to approve a biosimilar product, it must find that there are no clinically meaningful differences between the reference product and proposed biosimilar product in terms of safety, purity and potency. For the FDA to approve a biosimilar product as interchangeable with a reference product, the agency must find that the biosimilar product can be expected to produce the same clinical results as the reference product, and (for products administered multiple times) that the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic.

Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date of approval of the reference product. The FDA may not approve a biosimilar product until 12 years from the date on which the reference product was approved. Even if a product is considered to be a reference product eligible for exclusivity, another company could market a competing version of that product if the FDA approves a full BLA for such product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of their product. The BPCIA also created certain exclusivity periods for biosimilars approved as interchangeable products. At this juncture, it is unclear whether products deemed "interchangeable" by the FDA will, in fact, be readily substituted by pharmacies, which are governed by state pharmacy law. Since the passage of the BPCIA, many states have passed laws or amendments to laws, including laws governing pharmacy practices, which are state regulated, to regulate the use of biosimilars.

Post-Approval Regulation

If regulatory approval for marketing of a product or new indication for an existing product is obtained, the sponsor will be required to comply with all regular post-approval regulatory requirements as well as any post-approval requirements that the FDA have imposed as part of the approval process. The sponsor will be required to report certain adverse reactions and production problems to the FDA, provide updated safety and efficacy information, and comply with requirements concerning advertising and promotional labeling requirements. Manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with ongoing regulatory requirements, including cGMP regulations, which impose certain procedural and documentation requirements upon manufacturers, and applicable product tracking and tracing requirements. Accordingly, the sponsor and its third-party manufacturers must continue to expend time, money and effort in the areas of production and quality control to maintain compliance with cGMP regulations and other regulatory requirements.

A biological product may also be subject to official lot release, meaning that the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official lot release, the manufacturer must submit samples of each lot, together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot, to the FDA. The FDA may in addition perform certain confirmatory tests on lots of some products before releasing the lots for distribution. Finally, the FDA will conduct laboratory research related to the safety, purity, potency and effectiveness of pharmaceutical products.

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. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or

imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

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

The FDA strictly regulates the marketing, labeling, advertising and promotion of prescription drug products placed on the market. This regulation includes, among other things, standards and regulations for direct-to-consumer advertising, communications regarding unapproved uses, industry-sponsored scientific and educational activities and promotional activities involving the Internet and social media. Promotional claims about a drug's safety or effectiveness are prohibited before the drug is approved. After approval, a drug product generally may not be promoted for uses or patient populations that are not approved by the FDA, as reflected in the product's prescribing information (known as "off-label" use). In the United States, healthcare professionals are generally permitted to prescribe drugs for such off-label uses because the FDA does not regulate the practice of medicine. However, FDA regulations impose rigorous restrictions on manufacturers' communications, prohibiting the promotion of off-label uses.

If a company, including any agent of the company or anyone speaking on behalf of the company, is found to have promoted off-label uses, the company may become subject to adverse public relations and administrative and judicial enforcement by the FDA, the DOJ, or the Office of the Inspector General of the Department of Health and Human Services, as well as state authorities. This could subject a company to a range of penalties that could have a significant commercial impact, including civil and criminal fines and agreements that materially restrict the manner in which a company promotes or distributes drug products. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed.

Federal and State Data Privacy and Security Laws

Under the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA), the U.S. Department of Health and Human Services (HHS), has issued regulations to protect the privacy and security of protected health information (PHI), used or disclosed by covered entities including certain healthcare providers, health plans and healthcare clearinghouses. HIPAA also regulates standardization of data content, codes and formats used in healthcare transactions and standardization of identifiers for health plans and providers. HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 or HITECH, and their regulations, including the final omnibus rule published on January 25, 2013, also imposes certain obligations on the business associates of covered entities that obtain protected health information in providing services to or on behalf of covered entities. In addition to federal privacy regulations, there are a number of state laws governing confidentiality and security of health information that are applicable to our business. In addition to possible federal administrative, civil and criminal penalties for HIPAA violations, state attorneys general are authorized to file civil actions for damages or injunctions in federal courts to enforce HIPAA and seek attorney's fees and costs associated with pursuing federal civil actions. Accordingly, state attorneys general have brought civil actions seeking injunctions and damages resulting from alleged violations of HIPAA's privacy and security rules. New laws and regulations governing privacy and security may be adopted in the future as well.

Additionally, states, such as California, Virginia and Colorado have recently enacted the consumer privacy laws that grant rights to data subjects and place increased privacy and security obligations on entities handling personal data of consumers or households. While we are not currently subject to laws such as the California Consumer Privacy Act

(CCPA), some observers note that the CCPA and similar legislation could mark the beginning of a trend toward more stringent privacy legislation in the U.S., which could increase our potential liability and adversely affect our business.

Because of the breadth of these laws and the narrowness of the statutory exceptions under such laws, it is possible that some of our current or future business activities, including certain clinical research, sales and marketing practices and the provision of certain items and services to our customers, could be subject to challenge under one or more of such privacy and data security laws. The heightening compliance environment and the need to build and maintain robust and secure systems to comply with different privacy compliance and/or reporting requirements in multiple jurisdictions could increase the possibility that we may fail to comply fully with one or more of these requirements. If our operations are found to be in violation of any applicable privacy or data security laws or regulations, we may be subject to penalties, including potentially significant criminal, civil and administrative penalties, damages, fines, imprisonment, contractual damages, reputational harm, diminished profits and future earnings, additional reporting requirements and/or oversight if we become subject to a consent decree or similar agreement to resolve allegations of non-compliance with these laws, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. To the extent that we collect or otherwise process personal information, we may be subject to privacy or data protection laws that are in effect in such third countries foreign laws.

Regulation and Procedures Governing Approval of Medicinal Products Outside the United States

In order to market any product outside of the United States, a company must also comply with numerous and varying regulatory requirements of other countries and jurisdictions regarding quality, safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of products. Whether or not it obtains FDA approval for a product, an applicant will need to obtain the necessary approvals by the comparable foreign regulatory authorities before it can commence clinical trials or marketing of the product in those countries or jurisdictions. For example, the process governing approval of medicinal products in the European Union generally follows the same lines as in the United States. It entails satisfactory completion of preclinical studies and adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each proposed indication. It also requires the submission to the relevant competent authorities of a marketing authorization application (MAA) and granting of a marketing authorization by these authorities before the product can be marketed and sold in the European Union.

Clinical Trial Approval

In April 2014, the European Union adopted the new Clinical Trials Regulation (EU) No 536/2014, which came into effect on January 31, 2022 and repealed the Clinical Trials Directive 2001/20/EC. The transitory provisions of the Clinical Trials Regulation offer sponsors the possibility to choose between the requirements of the previous Clinical Trials Directive and the new Clinical Trials Regulation if the request for authorization of a clinical trial is submitted in the year after the Clinical Trials Regulation became applicable. If the sponsor chooses to submit under the Clinical Trials Directive, the clinical trial continues to be governed by the Clinical Trial Directive until three years after the Clinical Trials Regulation became applicable. If a clinical trial continues for more than three years after the Clinical Trial Regulation became applicable, the Clinical Trial Regulation will at that time begin to apply to the clinical trial. The Clinical Trial Regulation overhauls the current system of approvals for clinical trials in the European Union. Specifically, the new legislation, which is directly applicable in all EU Member States (meaning no national implementing legislation in each Member State is required), aims at simplifying and streamlining the approval of clinical trials in the European Union, simplifying adverse-event reporting procedures, improving the supervision of clinical trials and increasing their transparency. The main characteristics of the regulation include: a streamlined application procedure via a single-entry point through the Clinical Trials Information System (CTIS); a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts (Part I contains scientific and medicinal product documentation and Part II contains the national and patient-level documentation). Part I is assessed by a coordinated review by the competent authorities of all EU Member States in which an application for authorization of a clinical trial has been submitted (Member States concerned) of a draft report prepared by a Reference Member State. Part II is assessed separately by each Member State concerned. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the concerned EU Member State. However, overall related timelines will

be defined by the Clinical Trials Regulation. Parties conducting certain clinical trials must, as in the United States, post clinical trial information in the European Union at the EudraCT website: https://eudract.ema.europa.eu.

PRIME Designation in the European Union

In March 2016, the European Medicines Agency (EMA) launched an initiative to facilitate development of therapeutic candidates in indications, often rare, for which few or no therapies currently exist. The PRIority MEdicines (PRIME), scheme is intended to encourage drug development in areas of unmet medical need and provides accelerated assessment of products representing substantial innovation reviewed under the centralized procedure. Eligible products must target conditions for which there is an unmet medical need (there is no satisfactory method of diagnosis, prevention or treatment in the European Economic Area (EEA) or, if there is, the new medicine will bring a major therapeutic advantage) and they must demonstrate the potential to address the unmet medical need by introducing new methods of therapy or improving existing ones. Products from small- and medium-sized enterprises may qualify for earlier entry into the PRIME scheme than larger companies. Many benefits accrue to sponsors of therapeutic candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other development program elements, and accelerated marketing authorization application assessment once a dossier has been submitted. Importantly, a dedicated EMA contact and rapporteur from the Committee for Human Medicinal Products (CHMP), or Committee for Advanced Therapies are appointed early in the PRIME scheme facilitating increased understanding of the product at the EMA's Committee level. A kick-off meeting initiates these relationships and includes a team of multidisciplinary experts at the EMA to provide guidance on the overall development and regulatory strategies. Where, during the course of development, a medicine no longer meets the eligibility criteria, support under the PRIME scheme may be withdrawn.

Marketing Authorization

To obtain a marketing authorization for a product under the European Union regulatory system, an applicant must submit a Marketing Authorization Application (MAA), either under a centralized procedure administered by the EMA or one of the procedures administered by competent authorities in European Union Member States (decentralized procedure, national procedure, or mutual recognition procedure). A marketing authorization may be granted only to an applicant established in the European Union. Regulation (EC) No 1901/2006 provides that prior to obtaining a marketing authorization in the European Union, an applicant must demonstrate compliance with all measures included in an EMA-approved Pediatric Investigation Plan (PIP), covering all subsets of the pediatric population, unless the EMA has granted a product-specific waiver, class waiver or a deferral for one or more of the measures included in the PIP. The Paediatric Committee of the EMA (PDCO), may grant deferrals for some medicines, allowing a company to delay development of the medicine for children until there is enough information to demonstrate its effectiveness and safety in adults. The PDCO may also grant waivers when development of a medicine for children is not needed or is not appropriate, such as for diseases that only affect the elderly population. The respective requirements for all marketing authorization procedures are laid down in Regulation (EC) No 1901/2006, the so-called Paediatric Regulation. This requirement also applies when a company wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorized. Products that are granted a marketing authorization with the results of the pediatric clinical trials conducted in accordance with the PIP (even where such results are negative) are eligible for six months' supplementary protection certificate extension. In the case of orphan medicinal products, a two-year extension of the orphan market exclusivity may be available. This pediatric reward is subject to specific conditions and is not automatically available when data in compliance with the PIP are developed and submitted.

The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid for all European Union member states. Pursuant to Regulation (EC) No. 726/2004, the centralized procedure is compulsory for specific products, including for medicines produced by certain biotechnological processes, products designated as orphan medicinal products, advanced therapy products and products with a new active substance indicated for the treatment of certain diseases, including products for the treatment of cancer. The centralized procedure is optional for products containing a new active substance not yet authorized in the EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the European Union. Manufacturers must demonstrate the quality, safety and efficacy of their products to the EMA, which provides an opinion regarding the MAA. The European Commission grants or refuses marketing authorization in light of the opinion delivered by the EMA.

Under the centralized procedure, the CHMP established at the EMA is responsible for conducting an initial assessment of a product. Under the centralized procedure in the European Union, the maximum timeframe for the evaluation of an MAA is 210 days, excluding clock stops when additional information or written or oral explanation is to be provided by the applicant in response to questions of the CHMP. Clock stops may extend the timeframe of evaluation of a Marketing Authorization (MA) application considerably beyond 210 days. Where the CHMP gives a positive opinion, the EMA provides the opinion together with supporting documentation to the European Commission, who make the final decision to grant a marketing authorization, which is issued within 67 days of receipt of the EMA's recommendation. Accelerated evaluation may be granted by the CHMP in exceptional cases, when a medicinal product is of major interest from the point of view of public health and, in particular, from the viewpoint of therapeutic innovation. If the CHMP accepts such a request, the time limit of 210 days will be reduced to 150 days, but it is possible that the CHMP may revert to the standard time limit for the centralized procedure if it determines that it is no longer appropriate to conduct an accelerated assessment.

National MAs, which are issued by the competent authorities of the Member States of the EEA and only cover their respective territory, are available for products not falling within the mandatory scope of the centralized procedure. Where a product has already been authorized for marketing in a Member State of the EEA, this national MA can be recognized in other Member States through the mutual recognition procedure. If the product has not received a national MA in any Member State at the time of application, it can be approved simultaneously in various Member States through the decentralized procedure. Under the decentralized procedure an identical dossier is submitted to the competent authorities of each of the Member States in which the MA is sought, one of which is selected by the applicant as the Reference Member State (RMS). The competent authority of the RMS prepares a draft assessment report, a draft summary of the product characteristics (SmPC), and a draft of the labeling and package leaflet, which are sent to the other Member States (referred to as the Concerned Member States (CMSs)) for their approval. If the CMSs raise no objections, based on a potential serious risk to public health, to the assessment, SmPC, labeling, or packaging proposed by the RMS, the product is subsequently granted a national MA in all the Member States (i.e., in the RMS and the CMSs).

Now that the UK (which comprises Great Britain and Northern Ireland) has left the European Union, Great Britain will no longer be covered by centralized MAs (under the Northern Irish Protocol, centralized MAs will continue to be recognized in Northern Ireland). All medicinal products with a current centralized MA were automatically converted to Great Britain MAs on January 1, 2021. For a period of two years from January 1, 2021, the Medicines and Healthcare Products Regulatory Agency (MHRA), the UK medicines regulator, may rely on a decision taken by the European Commission on the approval of a new marketing authorization in the centralized procedure, in order to more quickly grant a new Great Britain MA. A separate application will, however, still be required.

Regulatory Data Protection in the European Union

In the European Union, new chemical entities approved on the basis of a complete independent data package qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity pursuant to Regulation (EC) No 726/2004, as amended, and Directive 2001/83/EC, as amended. Data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic (abbreviated) application for a period of eight years. During the additional two-year period of market exclusivity, a generic marketing authorization application can be submitted, and the innovator's data may be referenced, but no generic medicinal product can be marketed until the expiration of the market exclusivity. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to authorization, is held to bring a significant clinical benefit in comparison with existing therapies. Even if a compound is considered to be a new chemical entity so that the innovator gains the prescribed period of data exclusivity, another company may market another version of the product if such company obtained marketing authorization based on an MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials.

Patent Term Extensions in the European Union and Other Jurisdictions

The European Union also provides for patent term extension through Supplementary Protection Certificates (SPCs). The rules and requirements for obtaining a SPC are similar to those in the United States. An SPC may extend the term of a patent for up to five years after its originally scheduled expiration date and can provide up to a maximum of

fifteen years of marketing exclusivity for a drug. In certain circumstances, these periods may be extended for six additional months if pediatric exclusivity is obtained; and in the case of orphan medicinal products, a two-year extension of the orphan market exclusivity may be available. Although SPCs are available throughout the European Union, sponsors must apply on a country-by-country basis. Similar patent term extension rights exist in certain other foreign jurisdictions outside the European Union.

Periods of Authorization and Renewals

A marketing authorization is valid for five years, in principle, and it may be renewed after five years on the basis of a reevaluation of the risk-benefit balance by the EMA or by the competent authority of the authorizing member state. To that end, the marketing authorization holder must provide the EMA or the competent authority with a consolidated version of the file in respect of quality, safety and efficacy, including all variations introduced since the marketing authorization was granted, at least six months before the marketing authorization ceases to be valid. Once renewed, the marketing authorization is valid for an unlimited period, unless the European Commission or the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal period. Any authorization that is not followed by the placement of the drug on the European Union market (in the case of the centralized procedure) or on the market of the authorizing member state within three years after authorization ceases to be valid.

Regulatory Requirements After Marketing Authorization

Following approval, the holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of the medicinal product, and must adhere in strict compliance with the applicable EU laws, regulations and guidance, including Directive 2001/83/EC, Directive 2003/94/EC, Regulation (EC) No 726/2004 and the European Commission Guidelines for Good Manufacturing Practice. These include compliance with the European Union's stringent pharmacovigilance or safety reporting rules, pursuant to which post-authorization studies and additional monitoring obligations can be imposed. In addition, the manufacturing of authorized products, for which a separate manufacturer's license is mandatory, must also be conducted in strict compliance with the EMA's GMP requirements and comparable requirements of other regulatory bodies in the European Union, which mandate the methods, facilities and controls used in manufacturing, processing and packing of drugs to assure their safety and identity.

Much like the Anti-Kickback Statue prohibition in the United States, the provision of benefits or advantages to physicians to induce or encourage the prescription, recommendation, endorsement, purchase, supply, order or use of medicinal products is also prohibited in the European Union. The provision of benefits or advantages to induce or reward improper performance generally is usually governed by the national anti-bribery laws of European Union Member States, and the Bribery Act 2010 in the UK. Infringement of these laws could result in substantial fines and imprisonment. EU Directive 2001/83/EC, which is the EU Directive governing medicinal products for human use, further provides that, where medicinal products are being promoted to persons qualified to prescribe or supply them, no gifts, pecuniary advantages or benefits in kind may be supplied, offered or promised to such persons unless they are inexpensive and relevant to the practice of medicine or pharmacy. This provision has been transposed into the Human Medicines Regulations 2012 and so remains applicable in the UK despite its departure from the European Union.

Payments made to physicians in certain European Union Member States must be publicly disclosed. Moreover, agreements with physicians often must be the subject of prior notification and approval by the physician's employer, his or her competent professional organization and/or the regulatory authorities of the individual EU Member States. These requirements are provided in the national laws, industry codes or professional codes of conduct, applicable in the EU Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment.

Orphan Drug Designation and Exclusivity

Regulation (EC) No 141/2000 and Regulation (EC) No. 847/2000 provide that a product can be designated as an orphan drug by the European Commission if its sponsor can establish: that the product is intended for the diagnosis, prevention or treatment of (1) a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the European Union when the application is made, or (2) a life-threatening, seriously debilitating or serious and chronic condition in the European Union and that without incentives it is unlikely that the marketing of the

drug in the European Union would generate sufficient return to justify the necessary investment. For either of these conditions, the applicant must demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized in the European Union or, if such method exists, the drug will be of significant benefit to those affected by that condition.

An orphan drug designation provides a number of benefits, including fee reductions, regulatory assistance and the possibility to apply for a centralized European Union marketing authorization. Marketing authorization for an orphan drug leads to a ten-year period of market exclusivity being granted following marketing approval of the orphan product. During this market exclusivity period, neither the EMA nor the European Commission or the member states may only grant marketing authorization to a "similar medicinal product" for the same therapeutic indication if: (i) a second applicant can establish that its product, although similar to the authorized product, is safer, more effective or otherwise clinically superior; (ii) the marketing authorization holder for the authorized product consents to a second orphan medicinal product application; or (iii) the marketing authorization holder for the authorized product cannot supply enough orphan medicinal product. A "similar medicinal product" is defined as a medicinal product containing a similar active substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same therapeutic indication. The market exclusivity period for the authorized therapeutic indication may, however, be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan drug designation because, for example, the product is sufficiently profitable not to justify market exclusivity. Orphan drug designation must be requested before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The aforementioned EU rules are generally applicable in the European Economic Area (EEA), which consists of the EU Member States, plus Norway, Liechtenstein and Iceland.

Brexit and the Regulatory Framework in the United Kingdom

In June 2016, the electorate in the UK voted in favor of leaving the European Union (commonly referred to as Brexit). Thereafter, in March 2017, the country formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty and the UK formally left the European Union on January 31, 2020. A transition period began on February 1, 2020, during which EU pharmaceutical law remained applicable to the UK, which ended on December 31, 2020. Since the regulatory framework in the UK covering the quality, safety and efficacy of medicinal products, clinical trials, marketing authorization, commercial sales and distribution of medicinal products is derived from EU Directives and Regulations, Brexit could materially impact the future regulatory regime which applies to products and the approval of therapeutic candidates in the UK, as UK legislation now has the potential to diverge from EU legislation. It remains to be seen how Brexit will impact regulatory requirements for therapeutic candidates and products in the UK in the long-term.

Since the regulatory framework for pharmaceutical products in the United Kingdom covering quality, safety and efficacy of pharmaceutical products, clinical trials, marketing authorization, commercial sales and distribution of pharmaceutical products is derived from European Union directives and regulations, Brexit could materially impact the future regulatory regime that applies to products and the approval of therapeutic candidates in the United Kingdom. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, may force us to restrict or delay efforts to seek regulatory approval in the United Kingdom for any therapeutic candidates we may develop, which could significantly and materially harm our business.

In addition, once we begin to conduct business in the United Kingdom, we will be subject to stringent data protection laws that are in effect in the United Kingdom. As of January 1, 2021, the United Kingdom's European Union (Withdrawal) Act 2018 incorporated the GDPR (as it existed on December 31, 2020 but subject to certain UK specific amendments) into UK law, referred to as the UK GDPR. The UK GDPR and the UK Data Protection Act 2018 set out the United Kingdom's data protection regime, which is independent from but aligned to the European Union's data protection regime. Non-compliance with the UK GDPR may result in monetary penalties of up to £17.5 million or 4% of worldwide revenue, whichever is higher.

General Data Protection Regulation

Once we begin processing of personal data regarding individuals in the European Union, including personal health data, our activities will be subject to the GDPR, which became effective on May 25, 2018. The GDPR is wide-

ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, providing notification of data breaches, and taking certain measures when engaging third-party processors. The GDPR also imposes strict rules on the transfer of personal data to countries outside the European Union, including the United States, and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20 million or 4% of annual global revenues, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies and obtain compensation for damages resulting from violations of the GDPR. Compliance with the GDPR will be a rigorous and time-intensive process that may increase the cost of doing business or require us to change our business practices to ensure full compliance.

Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any therapeutic candidates for which we may seek regulatory approval by the FDA or other government authorities. In the United States and markets in other countries, patients who are prescribed treatments for their conditions and providers performing the prescribed services generally rely on third-party payers to reimburse all or part of the associated healthcare costs. Patients are unlikely to use any therapeutic candidates we may develop unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of such therapeutic candidates. Even if any therapeutic candidates we may develop are approved, sales of such therapeutic candidates will depend, in part, on the extent to which third-party payers, including government health programs in the United States such as Medicare and Medicaid, commercial health insurers and managed care organizations, provide coverage and establish adequate reimbursement levels for, such therapeutic candidates. The process for determining whether a payer will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payer will pay for the product once coverage is approved. Third-party payers are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost-effectiveness of medical products and services and imposing controls to manage costs. Third-party payers may limit coverage to specific products on an approved list, also known as a formulary, which might not include all of the approved products for a particular indication. For more information, see “Risks Related to Commercialization of Our Therapeutic Candidates”.

In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of the product, in addition to the costs required to obtain FDA or other comparable marketing approvals. Nonetheless, therapeutic candidates may not be considered medically necessary or cost effective. A decision by a third-party payer not to cover any therapeutic candidates we may develop could reduce physician utilization of such therapeutic candidates once approved and have a material adverse effect on our sales, results of operations and financial condition. Additionally, a payer’s decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Further, one payer’s determination to provide coverage for a product does not assure that other payers will also provide coverage and reimbursement for the product, and the level of coverage and reimbursement can differ significantly from payer to payer. Third-party reimbursement and coverage may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development. In addition, any companion diagnostic tests require coverage and reimbursement separate and apart from the coverage and reimbursement for their companion pharmaceutical or biological products. Similar challenges to obtaining coverage and reimbursement, applicable to pharmaceutical or biological products, will apply to any companion diagnostics.

The containment of healthcare costs also has become a priority of federal, state and foreign governments and the prices of pharmaceuticals have been a focus in this effort. Governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on 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 a company’s revenue generated from the sale of any approved products. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which a company or its collaborators receive marketing approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Outside the United States, ensuring adequate coverage and payment for any therapeutic candidates we may develop will face challenges. Pricing of prescription pharmaceuticals is subject to governmental control in many countries. Pricing negotiations with governmental authorities can extend well beyond the receipt of regulatory marketing approval for a product and may require us to conduct a clinical trial that compares the cost effectiveness of any therapeutic candidates we may develop to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in our commercialization efforts.

In the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular product candidate to currently available therapies (so called health technology assessments) in order to obtain reimbursement or pricing approval. For example, the European Union provides options for its member states to restrict the range of products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. European Union member states may approve a specific price for a product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the product on the market. Other member states allow companies to fix their own prices for products but monitor and control prescription volumes and issue guidance to physicians to limit prescriptions. Recently, many countries in the European Union have increased the amount of discounts required on pharmaceuticals and these efforts could continue as countries attempt to manage healthcare expenditures, especially in light of the severe fiscal and debt crises experienced by many countries in the European Union. The downward pressure on healthcare costs in general, particularly prescription products, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. Political, economic and regulatory developments may further complicate pricing negotiations and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various European Union member states, and parallel trade (arbitrage between low-priced and high-priced member states), can further reduce prices. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products, if approved in those countries.

Healthcare Law and Regulation

Pharmaceutical companies are subject to additional healthcare regulation and enforcement by the federal government and by authorities in the states and foreign jurisdictions in which they conduct their business that may constrain the financial arrangements and relationships through which we research, as well as sell, market and distribute any products for which we obtain marketing authorization. Such laws include, without limitation, state and federal anti-kickback, fraud and abuse, false claims, and transparency laws and regulations related to drug pricing and payments and other transfers of value made to physicians and other healthcare providers. If our operations are found to be in violation of any such laws or any other governmental regulations that apply, we may be subject to penalties, including, without limitation, administrative, civil and criminal penalties, damages, fines, disgorgement, the curtailment or restructuring of operations, integrity oversight and reporting obligations, exclusion from participation in federal and state healthcare programs and responsible individuals may be subject to imprisonment. For more information, see “Risks Related to Our Business Operations and Industry”.

Healthcare Reform

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. There have been a number of federal and state proposals during the last few years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and other medical products, government control and other changes to the healthcare system in the United States. For more information, see “Risks Related to Our Business Operations and Industry”.

By way of example, the United States and state governments continue to propose and pass legislation designed to reduce the cost of healthcare. In March 2010, the United States Congress enacted the ACA, which, among other things, includes changes to the coverage and payment for products under government healthcare programs. The ACA, among other things, subjected biologic products to potential competition by lower-cost biosimilars; addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected; increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; extended the Medicaid Drug Rebate program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations; subjected manufacturers to new annual

fees and taxes for certain branded prescription drugs; created a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (increased to 70% pursuant to the Bipartisan Budget Act of 2018, effective as of January 1, 2019) point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D; and provided incentives to programs that increase the federal government's comparative effectiveness research.

Since enactment of the ACA, there have been, and continue to be, numerous judicial, administrative, executive, and legislative challenges to certain aspects of the ACA. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court's decision, President Biden issued an Executive Order to initiate a special enrollment period from February 15, 2021 through August 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The Executive Order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is unclear how other healthcare reform measures of the Biden administrations or other efforts, if any, to challenge repeal or replace the ACA, will impact our business.

Other legislative changes have been proposed and adopted in the United States since the Affordable Care Act was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers up to 2% per fiscal year, and, due to subsequent legislative amendments, will remain in effect through 2030 unless additional Congressional action is taken. Pursuant to the Coronavirus Aid, Relief, and Economic Security Act, also known as the CARES Act, as well as subsequent legislation, these reductions have been suspended from May 1, 2020 through March 31, 2022 due to the ongoing COVID-19 pandemic. Following the temporary suspension, a 1% payment reduction will occur beginning April 1, 2022 through June 30, 2022, and the 2% payment reduction will resume on July 1, 2022.

Human Capital Resources

As of February 28, 2022, we had 114 full-time employees, including a total of 47 employees with Ph.D. degrees. Of these full-time employees, 86 employees are engaged in research and development. None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

Our human capital resources objectives include, as applicable, identifying, recruiting, retaining, incentivizing and integrating our existing and new employees. The principal purposes of our equity and cash incentive plans are to attract, retain and reward personnel, whether existing employees or new hires, through the granting of stock-based and cash-based compensation awards. We believe that this increases value to our stockholders and the success of our company by motivating such individuals to perform to the best of their abilities and achieve our objectives.

We have, since our inception, worked to create a high-performing, inclusive and diverse workforce, which is a core element of our operating culture. We have deliberately sought to secure top talent with a diversity of thought, experiences and backgrounds who are committed to making a difference in the lives of patients with neuroscience diseases. We believe that, by embracing differences, we have a unique advantage in challenging the status quo to apply innovative thinking to long-existing medical challenges. As of February 28, 2022, our workforce was self-reportedly approximately 49% women and approximately 52% Asian, Hispanic, Latino, Black or African American, and our senior leadership was 68% women or minorities, reflecting the workforce we strive to create throughout the company.

As the success of our business is fundamentally connected to the well-being of our employees, we are committed to their health, safety and wellness. We provide our employees and their families with access to convenient health and wellness programs, including benefits that provide protection and security giving them peace of mind concerning events that may require time away from work or that impact their financial well-being; and that offer choices where possible so they can customize their benefits to meet their needs and the needs of their families. In response to the ongoing COVID-19 pandemic, we implemented significant changes that we determined were in the best interest of our

employees, as well as the community in which we operate, and which comply with government regulations, including working in a remote environment where appropriate or required.

Available Information

We maintain an internet website at www.entradatx.com and make available free of charge through our website our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, including exhibits and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Exchange Act of 1934, or the Exchange Act. We make these reports available through our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the SEC. You can review our electronically filed reports and other information that we file with the SEC on the SEC's web site at http://www.sec.gov. We also make available, free of charge on our website, the reports filed with the SEC by our executive officers, directors and 10% stockholders pursuant to Section 16 under the Exchange Act as soon as reasonably practicable after copies of those filings are provided to us by those persons. In addition, we regularly use our website to post information regarding our business, product development programs and governance, and we encourage investors to use our website, particularly the information in the section entitled "Investor Relations," as a source of information about us.

The information on our website is not incorporated by reference into this Annual Report on Form 10-K and should not be considered to be a part of this Annual Report on Form 10-K. Our website address is included in this Annual Report on Form 10-K as an inactive technical reference only.

Note Regarding Trademarks

We have applied for various trademarks that we use in connection with the operation of our business. This Annual Report may also contain trademarks, service marks and trade names of third parties, which are the property of their respective owners. Our use or display of third parties' trademarks, service marks, trade names or products in this Annual Report is not intended to, and does not imply a relationship with, or endorsement or sponsorship by us. Solely for convenience, the trademarks, service marks and trade names referred to in this Annual Report may appear without the ®, TM or SM symbols, but the omission of such references is not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or that the applicable owner of these trademarks, service marks and trade names will not assert, to the fullest extent under applicable law, its rights.

Item 1A. Risk Factors

In evaluating the Company and our business, careful consideration should be given to the following risk factors, in addition to the other information set forth in this Annual Report on Form 10-K (Annual Report) and in other documents that we file with the SEC. Investing in our common stock involves a high degree of risk. If any of the following risks are realized, our business, financial condition, results of operations and prospects could be materially and adversely affected. In that event, the trading price of our common stock could decline and you could lose part or all of your investment. Unless otherwise indicated, reference in this section and elsewhere in this Annual Report to our business being adversely affected, negatively impacted or harmed will include an adverse effect on, or a negative impact or harm to, the business, reputation, financial condition, results of operations, revenue and our future prospects. The material and other risks and uncertainties summarized above and described below are not intended to be exhaustive and are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial may also impair our business operations. This Annual Report 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 a number of factors, including the risks described below. See the section titled "Cautionary Note Regarding Forward-Looking Statements."

Risks Related to Our Limited Operating History, Financial Position and Capital Requirements

We have a limited operating history, have incurred significant operating losses since our inception and expect to incur significant losses for the foreseeable future. We may never generate any revenue or become profitable or, if we achieve profitability, we may not be able to sustain it.

Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. We are a preclinical-stage biopharmaceutical company with a limited operating history upon which our stockholders can evaluate our business and prospects. All of our development programs, including our lead therapeutic candidate, ENTR-601-44, are in preclinical development or in the drug discovery stage. We commenced operations in 2016, and to date, we have focused primarily on organizing and staffing our company, business planning, raising capital, developing our proprietary, highly versatile and modular EEV platform (EEV Platform), identifying EEV therapeutic candidates, establishing our intellectual property portfolio and conducting research and preclinical studies. Our approach to the discovery and development of therapeutic candidates based on our EEV Platform is unproven, and we do not know whether we will be able to conduct clinical studies on our therapeutic candidates, develop any therapeutic candidates that succeed in clinical development or produce products of commercial value. As an organization, we have not yet initiated or completed any clinical trials, obtained regulatory approvals, manufactured a clinical- or commercial-scale product, or arranged for a third party to do so on our behalf, or conducted sales and marketing activities necessary for successful product commercialization. Consequently, any predictions made about our future success or viability may not be as accurate as they could be if we had a history of successfully developing and commercializing biopharmaceutical products.

We have incurred significant operating losses since our inception. We do not have any products approved for sale and have not generated any product revenue since our inception. If our therapeutic candidates are not successfully developed and approved, we may never generate any significant revenue. Our net losses were $51.2 million and $26.5 million for the years ended December 31, 2021 and December 31, 2020, respectively. As of December 31, 2021, we had an accumulated deficit of $93.7 million. 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. All of our therapeutic candidates will require substantial additional development time and resources before we would be able to apply for or receive regulatory approvals and begin generating revenue from product sales. We expect to continue to incur losses for the foreseeable future, and we anticipate these losses will increase substantially as we continue our development of, seek regulatory approval for and potentially commercialize any of our therapeutic candidates.

To become and remain profitable, we must succeed in developing and eventually commercializing products that generate significant revenue. This will require us to be successful in a range of challenging activities, including completing preclinical studies and clinical trials of our therapeutic candidates, identifying lead therapeutic candidates, discovering additional therapeutic candidates, conducting preclinical studies prior to submitting an Investigational New Drug application (IND), obtaining clearance for an IND, obtaining regulatory approval for these therapeutic candidates and manufacturing, marketing and selling any products for which we may obtain regulatory approval. We are only in the preliminary stages of most of these activities. We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to achieve profitability. In addition, we have not yet demonstrated an ability to successfully overcome many of the risks and uncertainties frequently encountered by companies in new and rapidly evolving fields, particularly in the biopharmaceutical industry. Because of the numerous risks and uncertainties associated with biopharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able 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 may have an adverse effect on the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our therapeutic candidates or even continue our operations. A decline in the value of our company could also cause our stockholders to lose all or part of their investment.

Our limited operating history may make it difficult to evaluate our technology and industry and predict our future performance. Though several groups have conducted or are conducting studies involving the intracellular delivery of therapeutic molecules, the relevance of those studies to the evaluation of therapeutic candidates developed using our EEV Platform may be difficult to ascertain. Our short history as an operating company and novel therapeutic approach make any assessment of our future success or viability subject to significant uncertainty. We will encounter risks and difficulties frequently experienced by early-stage companies in rapidly evolving fields. Failure to address these risks successfully will cause our business to suffer. Similarly, we expect that our financial condition and operating results will fluctuate significantly from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. As a

result, our stockholders should not rely upon the results of any quarterly or annual period as an indicator of future operating performance.

In addition, as an early-stage company, we have encountered unforeseen expenses, difficulties, complications, delays and other known and unknown circumstances. As we advance our EEV therapeutic candidates, we will need to transition from a company with a research focus to a company capable of supporting clinical development and if successful, commercial activities. We may not be successful in such a transition.

We will require additional financing to achieve our goals, and a failure to obtain this necessary capital when needed on acceptable terms, or at all, could force us to delay, limit, reduce or terminate our development programs, commercialization efforts or other operations.

The development of biopharmaceutical therapeutic candidates is capital-intensive. We expect our expenses to increase in connection with our ongoing activities, particularly as we conduct our ongoing and planned preclinical studies of our development programs, initiate clinical trials for our therapeutic candidates and seek regulatory approval for our current therapeutic candidates and any future therapeutic candidates we may develop. If we obtain regulatory approval for any of our therapeutic candidates, we also expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution. Because the outcome of any preclinical study or clinical trial is highly uncertain, we cannot reasonably estimate the actual amounts necessary to successfully complete the development and commercialization of our therapeutic candidates. Furthermore, we expect to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. Failing to raise capital when needed or on attractive terms could force us to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

We believe that the net proceeds from our initial public offering completed in November 2021, together with our existing cash, cash equivalents and marketable securities, will enable us to fund our operations into the second half of 2024. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect. Our operating plans and other demands on our cash resources may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings or other capital sources, including potentially additional collaborations, licenses and other similar arrangements. In addition, we may seek additional capital due to favorable market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. Attempting to secure additional financing may divert our management from our day-to-day activities, which may adversely affect our ability to develop our therapeutic candidates. Our future capital requirements will depend on many factors, including, but not limited to:

- the type, number, scope, progress, expansions, results, costs and timing of our preclinical studies and any clinical trials of the therapeutic candidates that we are pursuing or may choose to pursue in the future;
- the clinical development plans we establish for our EEV therapeutic candidates;
- the costs and timing of manufacturing for our therapeutic candidates and commercial manufacturing if any therapeutic candidate is approved;
- the costs of establishing and maintaining clinical and commercial supply for the development and manufacture of our therapeutic candidates;
- the costs, timing and outcome of regulatory review of our therapeutic candidates;
- the terms and timing of establishing and maintaining collaborations, licenses and other similar arrangements;
- the costs of obtaining, maintaining and enforcing our patents and other intellectual property rights;
- our efforts to enhance operational systems and hire additional personnel to satisfy our obligations as a public company, including enhanced internal controls over financial reporting;

- the costs associated with hiring additional personnel and consultants as our preclinical and clinical activities increase;
- the achievement of milestones or occurrence of other developments that trigger payments under any collaboration agreements, if any;
- the costs and timing of establishing or securing sales and marketing capabilities if any therapeutic candidate is approved;
- subject to receipt of regulatory approval, revenue, if any, received from commercial sales of our therapeutic candidates;
- our ability to achieve sufficient market acceptance, coverage and adequate reimbursement from third-party payors and adequate market share and revenue for any approved products;
- the terms and timing of establishing and maintaining collaborations, licenses and other similar arrangements;
- the costs of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights, including enforcing and defending intellectual property related claims; and
- the ongoing costs of operating as a public company.

Identifying potential therapeutic candidates and conducting preclinical studies 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 regulatory approval and commercialize our therapeutic candidates. In addition, our therapeutic candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of products that we do not expect to be commercially available for many years, if at all.

Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all.

Our operating results may fluctuate significantly, which makes our future operating results difficult to predict and could cause our operating results to fall below expectations or our guidance.

Our quarterly and annual operating results may fluctuate significantly in the future, which makes it difficult for us to predict our future operating results. From time to time, we may enter into license or collaboration agreements or strategic partnerships with other companies that include development funding and significant upfront and milestone payments and/or royalties, which may become an important source of our revenue. These upfront and milestone payments may vary significantly from period to period and any such variance could cause a significant fluctuation in our operating results from one period to the next.

In addition, we measure compensation cost for stock-based awards made to employees at the grant date of the award, based on the fair value of the award as determined by our board of directors, and recognize the cost as an expense over the employee's requisite service period. As the variables that we use as a basis for valuing these awards change over time, including our underlying stock price and stock price volatility, the magnitude of the expense that we must recognize may vary significantly.

Furthermore, our operating results may fluctuate due to a variety of other factors, many of which are outside of our control and may be difficult to predict, including the following:

- the timing and cost of, and level of investment in, research and development activities relating to our programs, which will change from time to time;
- our ability to enroll patients in clinical trials and the timing of enrollment;

- the cost of manufacturing our current therapeutic candidates and any future therapeutic candidates, which may vary depending on FDA, EMA or other comparable foreign regulatory authority guidelines and requirements, the quantity of production and the terms of our agreements with manufacturers;
- expenditures that we will or may incur to acquire or develop additional therapeutic candidates and technologies or other assets;
- the timing and outcomes of preclinical studies and clinical trials for ENTR-601-44 and any therapeutic candidates from our discovery programs, or competing therapeutic candidates;
- the need to conduct unanticipated clinical trials or trials that are larger or more complex than anticipated;
- competition from existing and potential future products that compete with ENTR-601-44 or any of our discovery programs, and changes in the competitive landscape of our industry, including consolidation among our competitors or partners;
- any delays in regulatory review or approval of ENTR-601-44 or therapeutic candidates from any of our discovery programs;
- the level of demand for any of our therapeutic candidates, if approved, which may fluctuate significantly and be difficult to predict;
- the risk/benefit profile, cost and reimbursement policies with respect to our therapeutic candidates, if approved, and existing and potential future products that compete with ENTR-601-44 or any of our discovery programs;
- our ability to commercialize ENTR-601-44 or therapeutic candidates from any of our discovery programs, if approved, inside and outside of the U.S., either independently or working with third parties;
- our ability to establish and maintain collaborations, licensing or other arrangements;
- our ability to adequately support future growth;
- potential unforeseen business disruptions that increase our costs or expenses;
- future accounting pronouncements or changes in our accounting policies; and
- the changing and volatile global economic and political environment.

The cumulative effect of these factors could result in large fluctuations and unpredictability in our quarterly and annual operating results. As a result, comparing our operating results on a period-to-period basis may not be meaningful. Investors should not rely on our past results as an indication of our future performance. This variability and unpredictability could also result in our failing to meet the expectations of industry or financial analysts or investors for any period. If our revenue or operating results fall below the expectations of analysts or investors or below any forecasts we may provide to the market, or if the forecasts we provide to the market are below the expectations of analysts or investors, the price of our common stock could decline substantially. Such a stock price decline could occur even when we have met any previously publicly stated guidance we may provide.

Risks Related to the Discovery, Development and Regulatory Approval of Our Therapeutic Candidates

We are early in our development efforts. We have not initiated clinical studies, and as a result it will be years before we commercialize a therapeutic candidate, if ever. If we are unable to identify and advance therapeutic candidates through preclinical studies and clinical trials, obtain marketing approval and ultimately commercialize them, or experience significant delays in doing so, our business will be materially harmed.

We are early in our development efforts and all our development programs, including our lead therapeutic candidate ENTR-601-44, are in the preclinical or drug discovery stage. We have invested substantially all of our research efforts to date in developing our EEV Platform, identifying potential therapeutic candidates and conducting preclinical studies. As an organization, we have never conducted any clinical trials or submitted an application for regulatory approval, and we may be unable to do so for our therapeutic candidates. We have not yet completed IND-enabling studies for ENTR-601-44, our lead candidate, and we will need to do so to support submission of an IND and progress ENTR-601-44 into and through clinical studies. In addition, we have a development portfolio of programs that are in earlier stages of development and have not yet initiated or completed IND-enabling studies. We may never advance any therapeutic candidates through IND-enabling studies and receive authorization from the U.S. Food and Drug Administration (FDA), to proceed under an IND prior to initiating their clinical-stage development. 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 therapeutic candidates, which may never occur. We currently generate no revenue from sales of any product, and we may never be able to develop or commercialize a marketable product.

Commencing clinical trials in the United States is subject to acceptance by the FDA of an IND and finalizing the trial design based on discussions with the FDA and other regulatory authorities. For the FDA to accept an IND, we must complete Good Laboratory Practices (GLP) studies, which may not be successful or may take longer than we expect. The FDA may require us to complete additional preclinical studies or we may be required to satisfy other FDA requests prior to commencing clinical trials, and such requests may not currently be known or anticipated, which may cause the start of our first clinical trials to be delayed or prevent us from conducting clinical trials. Even after we receive and incorporate guidance from these regulatory authorities, the FDA or other regulatory authorities could disagree that we have satisfied their requirements to commence any clinical trial or change their position on the acceptability of our trial design or the clinical endpoints selected, which may require us to complete additional preclinical studies or clinical trials, impose stricter approval conditions than we currently expect or may prevent us from conducting clinical trials. There are equivalent processes and risks applicable to clinical trial applications in other countries, including countries in the European Union (EU).

Commercialization of any therapeutic candidates we may develop will require preclinical and clinical development; regulatory and marketing approval in multiple jurisdictions, including by the FDA and the European Medicines Agency (EMA); manufacturing supply, capacity and expertise; a commercial organization; and significant marketing efforts. The success of therapeutic candidates we may identify and develop will depend on many factors, including:

- timely and successful completion of preclinical studies, including toxicology studies, biodistribution studies and minimally efficacious dose studies in animals, where applicable;
- sufficiency of our financial and other resources to complete the necessary preclinical studies and clinical trials;
- effective INDs or comparable foreign applications that allow commencement of our planned clinical trials or future clinical trials for any therapeutic candidates we may develop;
- successful enrollment and completion of clinical trials, including under the FDA's current Good Clinical Practices (cGCPs), current Good Laboratory Practices (cGLPs) and any additional regulatory requirements from foreign regulatory authorities;
- positive results from our future clinical trials that support a finding of safety and effectiveness and an acceptable risk-benefit profile in the intended populations;
- receipt of regulatory marketing approvals from applicable regulatory authorities;

- establishment of arrangements with third-party manufacturers for clinical supply and, where applicable, commercial manufacturing capabilities;
- establishment, maintenance, defense and enforcement of patent, trademark, trade secret and other intellectual property protection or regulatory exclusivity for any therapeutic candidates we may develop;
- patient recruitment and enrollment;
- commercial launch of any therapeutic candidates we may develop, if approved, whether alone or in collaboration with others;
- acceptance of the benefits and use of our therapeutic candidates we may develop, including method of administration, if and when approved, by patients, the medical community and third-party payors;
- our ability to compete effectively with other therapies and treatment options;
- maintenance of a continued acceptable safety, tolerability and efficacy profile of any therapeutic candidates we may develop following approval; and
- establishment and maintenance of healthcare coverage and adequate reimbursement by payors.

If we do not succeed in one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize any therapeutic candidates we may develop, which would materially harm our business. If we are unable to advance our therapeutic candidates to clinical development, obtain regulatory approval and ultimately commercialize our therapeutic candidates, or experience significant delays in doing so, our business will be materially harmed.

Our business is highly dependent on the clinical advancement of our programs and modalities and is especially dependent on the success of our lead EEV therapeutic candidate, ENTR-601-44. Delay or failure to advance programs or modalities, including ENTR-601-44 could adversely impact our business.

Using our platform, we are developing product features for medicines based on EEVs. Over time, our platform work led to commonalities, where a specific combination of EEV technologies, delivery technologies, and manufacturing processes generated a set of product features shared by multiple programs, for example, oligonucleotide-conjugated EEVs and antibody-conjugated EEVs. This is what we call a "modality." We are utilizing early programs in a modality, such as ENTR-601-44 for oligonucleotide-conjugated EEVs, to understand the technology risks within the modality, including manufacturing and pharmaceutical properties. Our lead therapeutic candidate, ENTR-601-44, is being developed to address Duchenne muscular dystrophy (DMD) and we are highly dependent on the success of the future clinical trials of ENTR-601-44, the outcomes of which are uncertain, to further develop a second lead therapeutic candidate for patients with DMD with exon 45 skipping amenable mutations. Because ENTR-601-44 is our first EEV therapeutic candidate, if ENTR-601-44 encounters safety, efficacy, supply or manufacturing problems, developmental delays, regulatory or commercialization issues or other problems, the value of our EEV Platform could be greatly diminished and our development plans and business would be significantly harmed.

Even if our earlier programs in a modality are successful in any phase of development any of such earlier programs may fail at a later phase of development, and other programs within the same modality may still fail at any phase of development including at phases where earlier programs in that modality were successful. This may be a result of technical challenges unique to that program or due to biology risk, which is unique to every program. As we progress our programs through clinical development, there may be new technical challenges that arise that cause an entire modality to fail.

Our EEV therapeutic candidates are based on a novel therapeutic approach, which makes it difficult to predict the time and cost of development and of subsequently obtaining regulatory approval, if at all.

Using EEV technology to develop therapeutic candidates is a new therapeutic approach and no products based on EEVs have been approved to date in the United States, the United Kingdom or the EU. As such, it is difficult to accurately

predict the developmental challenges we may face for our EEV therapeutic candidates as they proceed through development. In addition, because we have not yet commenced any clinical trials with our EEV therapeutic candidates, we have not yet been able to assess safety in humans and there may be short-term or long-term effects from treatment with any therapeutic candidates that we develop that we cannot predict at this time. Also, animal models may not exist for some of the diseases we choose to pursue in our programs. As a result of these factors, it is more difficult for us to predict the time and cost of therapeutic candidate development and we cannot predict whether our EEV Platform, or any similar or competitive intracellular delivery technologies, will enable the identification, development and regulatory approval of any products. There can be no assurance that any development problems we experience in the future related to our EEV Platform or any of our research programs will not cause significant delays or unanticipated costs or that such development problems can be solved. Any of these factors may prevent us from completing our preclinical studies or any clinical trials that we may initiate or commercializing any therapeutic candidates we may develop on a timely or profitable basis, if at all.

The clinical trial requirements of the FDA and other regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a therapeutic candidate vary substantially according to the type, complexity, novelty and intended use and market of the therapeutic candidate. No products based on EEVs have been approved to date by regulators. As a result, the regulatory approval process for therapeutic candidates such as ours is uncertain and may be more expensive and take longer than the approval process for therapeutic candidates based on other, better known or more extensively studied technologies. For example, the general approach for FDA approval of a new biologic or drug is for sponsors to seek licensure or approval based on dispositive data from well-controlled, Phase 3 clinical trials of the relevant therapeutic candidate in the relevant patient population. Phase 3 clinical trials typically involve hundreds of patients, have significant costs and take years to complete. It is difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our therapeutic candidates in the U.S., the UK, the EU or other regions of the world or how long it will take to commercialize our therapeutic candidates. Delay or failure to obtain or unexpected costs in obtaining the regulatory approvals necessary to bring a potential therapeutic candidate to market could decrease our ability to generate sufficient product revenue and our business, financial condition, results of operations and prospects may be harmed.

Preclinical and clinical development involves a lengthy and expensive process with an uncertain outcome, and the results of preclinical studies are not necessarily predictive of the results of later preclinical studies and any clinical trials of our therapeutic candidates. We have not tested any of our therapeutic candidates in clinical trials and our therapeutic candidates may not have favorable results in clinical trials, if any, or receive regulatory approval on a timely basis, if at all.

Preclinical and clinical development is expensive and can take many years to complete, and its outcome is inherently uncertain. We cannot guarantee that any preclinical studies or clinical trials will be conducted as planned or completed on schedule, if at all, and failure can occur at any time during the preclinical study or clinical trial process. Any positive results from our preclinical studies of our EEV therapeutic candidates may not necessarily be predictive of the results in later preclinical studies and clinical trials. Similarly, even if we are able to complete our planned preclinical studies or clinical trials of our therapeutic candidates according to our current development timeline, the positive results from such preclinical studies and clinical trials may not be replicated in our subsequent preclinical studies or later-stage clinical trials. Despite promising preclinical or clinical results, any therapeutic candidate can unexpectedly fail at any stage of preclinical or clinical development. The historical failure rate for therapeutic candidates in our industry is high.

The results from preclinical studies or clinical trials of a therapeutic candidate may not predict the results of later clinical trials of the therapeutic candidate, and interim, topline, or preliminary results of a clinical trial are not necessarily indicative of final results. Therapeutic candidates in later stages of clinical trials may fail to show the desired safety and efficacy characteristics despite having progressed through preclinical studies and initial clinical trials. In particular, while we have conducted certain preclinical studies of ENTR-601-44 and other potential therapeutic candidates, we do not know whether ENTR-601-44 or the other potential therapeutic candidates will perform in future clinical trials as they have performed in these prior studies. The positive results we have observed for our therapeutic candidates in early, non-GLP preclinical studies and animal models may not be predictive of our future clinical trials in humans. Furthermore, for some indications that we are pursuing there are no animal models that adequately mirror the human disease to predict any level of positive results. It is not uncommon to observe results in clinical trials that are unexpected based on preclinical studies and early clinical trials, and many therapeutic candidates fail in clinical trials despite very promising early results. We are currently conducting IND-enabling studies for ENTR-601-44. Unexpected observations or toxicities observed in these studies, or in IND-enabling studies for any of our other development programs, could delay clinical trials for ENTR-601-44 or our other development programs. Moreover, preclinical and clinical data may be susceptible to varying interpretations and analyses. A number of companies in the biopharmaceutical and biotechnology industries have suffered significant

setbacks in clinical development even after achieving promising results in earlier studies, and companies that have believed their therapeutic candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain FDA approval. Additionally, we may conduct clinical trials that utilize an "open-label" trial design. An "open-label" clinical trial is one where both the patient and investigator know whether the patient is receiving the investigational therapeutic candidate or either an existing approved drug or placebo. Most typically, open-label clinical trials test only the investigational therapeutic candidate and sometimes may do so at different dose levels. Open-label clinical trials are subject to various limitations that may exaggerate any therapeutic effect as patients in open-label clinical trials are aware when they are receiving treatment. Open-label clinical trials may be subject to a "patient bias" where patients perceive their symptoms to have improved merely due to their awareness of receiving an experimental treatment. In addition, open-label clinical trials may be subject to an "investigator bias" where those assessing and reviewing the physiological outcomes of the clinical trials are aware of which patients have received treatment and may interpret the information of the treated group more favorably given this knowledge. The results from an open-label trial may not be predictive of future clinical trial results with any of our therapeutic candidates for which we include an open-label clinical trial when studied in a controlled environment with a placebo or active control.

For the foregoing reasons, we cannot be certain that our ongoing and planned preclinical studies and planned clinical trials will be successful. Any safety concerns observed in any one of our clinical trials in our targeted indications could limit the prospects for regulatory approval of our therapeutic candidates in those and other indications, which could have a material adverse effect on our business, financial condition and results of operations.

Substantial delays in the commencement, enrollment or completion of our planned clinical trials or failure to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities could prevent us from commercializing any therapeutic candidates we determine to develop on a timely basis, if at all.

The risk of failure in developing therapeutic candidates is high. It is impossible to predict when or if any therapeutic candidate would prove effective or safe in humans or will receive regulatory approval. Before obtaining marketing approval from regulatory authorities for the sale of any therapeutic candidate, we must complete preclinical development, submit an IND or foreign equivalent to permit initiation of clinical studies, and then conduct extensive clinical trials to demonstrate the safety and efficacy of therapeutic candidates in humans. We have not yet conducted a clinical trial of any therapeutic candidate. As an organization, we plan to advance ENTR-601-44 to IND submission in 2022 and to advance our EEV therapeutic candidate targeting exon 45 to IND submission in 2023. We have not previously conducted any clinical trials of any therapeutic candidates, have limited experience as a company in preparing, submitting and prosecuting regulatory filings and have not previously submitted an IND, NDA or BLA or other comparable foreign regulatory submission for any therapeutic candidate. In addition, we have had limited interactions with the FDA and cannot be certain how many clinical trials of ENTR-601-44 or any other therapeutic candidates will be required or how such trials should be designed. Consequently, we may be unable to successfully and efficiently execute and complete necessary clinical trials in a way that leads to regulatory submission and approval of any of our therapeutic candidates. Clinical trials may fail to demonstrate that our therapeutic candidates are safe for humans and effective for indicated uses. Even if the clinical trials are successful, changes in marketing approval policies during the development period, changes in or the enactment or promulgation of additional statutes, regulations or guidance or changes in regulatory review for each submitted product application may cause delays in the approval or rejection of an application.

Before we can commence clinical trials for a therapeutic candidate, we must complete extensive preclinical testing and studies that support our INDs and other regulatory filings. We cannot be certain of the timely identification of a therapeutic candidate or the completion or outcome of our preclinical testing and studies and cannot predict whether the FDA will accept our proposed clinical programs or whether the outcome of our preclinical testing and studies will ultimately support the further development of any therapeutic candidates. Conducting preclinical testing is a lengthy, time-consuming and expensive process. The length of time may vary substantially according to the type, complexity and novelty of the program, and often can be several years or more per program. As a result, we cannot be sure that we will be able to submit INDs for our preclinical programs on the timelines we expect, if at all, and we cannot be sure that submission of INDs will result in the FDA allowing clinical trials to begin.

Furthermore, therapeutic candidates are subject to continued preclinical safety studies, which may be conducted concurrently with our clinical testing. The outcomes of these safety studies may delay the launch of or enrollment in future clinical trials and could impact our ability to continue to conduct our clinical trials.

Clinical testing is expensive, is difficult to design and implement, can take many years to complete and is uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, or at all. A failure of one or more clinical trials can occur at any stage of testing, which may result from a multitude of factors, including, but not limited to, flaws in trial design, dose selection issues, patient enrollment criteria and failure to demonstrate favorable safety or efficacy traits.

Other events that may prevent successful enrollment, initiation or timely completion of clinical development include:

- we may be unable to generate sufficient preclinical, toxicology or other *in vivo* or *in vitro* data to support the initiation of clinical trials;
- delays in reaching a consensus with regulatory authorities on trial design;
- delays in reaching agreement on acceptable terms with prospective clinical research organizations (CROs) and clinical trial sites;
- delays in opening clinical trial sites or obtaining required institutional review board (IRB) or independent ethics committee approval, or the equivalent review groups for sites outside the United States, at each clinical trial site;
- we may need to add new or additional clinical trial sites;
- imposition of a clinical hold by regulatory authorities as a result of a serious adverse event or after an inspection of our clinical trial operations or trial sites;
- negative or inconclusive results observed in clinical trials, including failure to demonstrate statistical significance, safety, purity or potency, which could lead us, or cause regulators to require us, to conduct additional clinical trials or abandon product development programs;
- positive results from our preclinical studies of our therapeutic candidates may not necessarily be predictive of the results from required later preclinical studies and clinical trials and positive results from such preclinical studies and clinical trials of our therapeutic candidates may not be replicated in subsequent preclinical studies or clinical trial results;
- failure by us, any CROs we engage or any other third parties to adhere to clinical trial requirements;
- failure to perform in accordance with applicable cGCPs;
- failure by investigators to adhere to clinical trial protocols leading to variable results;
- delays in the testing, validation, manufacturing and delivery of any therapeutic candidates we may develop to the clinical sites, including delays by third parties with whom we have contracted to perform certain of those functions;
- failure of our third-party contractors to comply with regulatory requirements or to meet their contractual obligations to us in a timely manner, or at all;
- delays in having patients complete participation in a trial or return for post-treatment follow-up;
- clinical trial sites or patients dropping out of a trial;
- selection of clinical endpoints that require prolonged periods of clinical observation or analysis of the resulting data;

- occurrence of serious adverse events associated with the therapeutic candidate that are viewed to outweigh its potential benefits;
- occurrence of serious adverse events associated with a therapeutic candidate in development by another company, which are viewed to outweigh its potential benefits, and which may negatively impact the perception of our product due to a similarity in technology or approach;
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols;
- the FDA or other regulatory authorities may require us to submit additional data such as long-term toxicology studies or impose other requirements before permitting us to initiate a clinical trial;
- changes in the legal or regulatory regimes domestically or internationally related to patient rights and privacy; or
- lack of adequate funding to continue the clinical trial.

We could also encounter delays if a clinical trial is suspended, placed on clinical hold or terminated by us, the IRBs of the institutions in which such trials are being conducted, or the FDA or other regulatory authorities or recommended for suspension or termination by the Data Safety Monitoring Board (DSMB) for such trial. A suspension or termination may be imposed due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a product or treatment, failure to establish or achieve clinically meaningful trial endpoints, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. Many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our therapeutic candidates. Further, the FDA or other regulatory authorities may disagree with our clinical trial design and our interpretation of data from clinical trials, or may change the requirements for approval even after they have reviewed and commented on the design for our clinical trials. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses and many companies that believed their therapeutic candidates performed satisfactorily in preclinical studies and clinical trials nonetheless failed to obtain FDA approval.

Any inability to successfully complete preclinical studies and clinical trials could result in additional costs to us or impair our ability to generate revenues from product sales, regulatory and commercialization milestones and royalties. In addition, manufacturing or formulation changes to any therapeutic candidates we may develop may require us to conduct additional studies or trials to bridge our modified therapeutic candidates to earlier versions. Clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize any therapeutic candidates we may develop or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize any therapeutic candidates we may develop and may harm our business, financial condition, results of operations and prospects.

Additionally, if the results of future clinical trials are inconclusive or if there are safety concerns or serious adverse events associated with any therapeutic candidates we may develop, we may:

- be delayed in obtaining marketing approval for therapeutic candidates, if at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;
- be subject to changes in the way the product is administered;
- be required to perform additional clinical trials to support approval or be subject to additional post-marketing testing requirements;

- have regulatory authorities withdraw, or suspend, their approval of the product or impose restrictions on its distribution in the form of a modified risk evaluation and mitigation strategy;
- be subject to the addition of labeling statements, such as warnings or contraindications;
- be sued; or
- experience damage to our reputation.

Delays or difficulties in the enrollment of patients in clinical trials could delay or prevent our receipt of necessary regulatory approvals.

Failure to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or similar regulatory authorities outside the U.S. may delay or prevent us from initiating or continuing clinical trials for our therapeutic candidates. Because the target patient populations for some of our therapeutic candidates are relatively small, it may be difficult to successfully identify patients. Although we may enter into agreements with third parties to develop companion diagnostic tests for use in some of our future clinical trials in order to help identify eligible patients in certain indications, we may experience delays in reaching, or fail to reach, agreement on acceptable terms to develop such companion diagnostic tests. Any third parties whom we engage to develop companion diagnostic tests may experience delays or may not be successful in developing such companion diagnostic tests, furthering the difficulty in identifying patients for our clinical trials. In addition, current commercially available diagnostic tests to identify appropriate patients for our clinical trials or any approved therapeutic candidates may become unavailable in the future.

In addition, we may experience delays or disruptions in the initiation of or enrollment in our planned clinical trials due to the ongoing COVID-19 pandemic and changes in local site or IRB policies, availabilities of site staff, reprioritization of hospital resources, restricted access to healthcare professionals and testing sites and other containment measures or concerns among patients about participating in clinical trials during a pandemic. Furthermore, some of our competitors have ongoing clinical trials for therapeutic candidates that treat the same indications as our therapeutic candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' therapeutic candidates.

In addition, the pediatric population is an important patient population for certain of the indications we are targeting, including DMD, and our addressable patient population estimates include pediatric populations. However, it may be more challenging to conduct studies in this population, and to locate and enroll pediatric patients. Additionally, it may be challenging to ensure that pediatric or adolescent patients adhere to clinical trial protocols. Patient enrollment and trial competition may be affected by other factors including:

- clinicians' and patients' perceived risks and benefits of the therapeutic candidate under trial, particularly therapeutic candidates developed using a novel and unproven therapeutic approach, like our EEV therapeutic candidates in relation to available or investigational drugs;
- size of the patient population, in particular for rare diseases such as the diseases on which we are initially focused, and process for identifying patients;
- design of the trial protocol;
- efforts to facilitate timely enrollment in clinical trials;
- eligibility and exclusion criteria;
- availability of competing therapies and clinical trials;
- severity of the disease or disorder under investigation;
- proximity and availability of clinical trial sites for prospective patients;

- ability to obtain and maintain patient consent;
- risk that enrolled patients will drop out before completion of the trial;
- patient referral practices of physicians; and
- ability to monitor patients adequately during and after treatment.

Our inability to identify patients appropriate for enrollment in our clinical trials, or to enroll a sufficient number of patients in our clinical trials, would result in significant delays and could require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for our therapeutic candidates, which would cause the value of our company to decline and limit our ability to obtain additional financing. If we are unable to include patients with the driver of the disease, including the applicable genomic alteration for diseases in genomically defined patient populations, this could limit our ability to seek participation in the FDA's expedited development programs, including Breakthrough Therapy Designation and Fast Track Designation, or otherwise to seek to accelerate clinical development and regulatory timelines.

Even if we are able to enroll a sufficient number of patients for our clinical trials, we may have difficulty maintaining patients in our clinical trials. In our planned clinical trials that will include a placebo group, some of the patients who end up receiving placebo may perceive that they are not receiving the therapeutic candidate being tested, and they may decide to withdraw from our clinical trials to pursue other alternative therapies rather than continue the trial with the perception that they are receiving placebo. Difficulty enrolling or maintaining a sufficient number of patients to conduct our clinical trials, may require us to delay, limit or terminate clinical trials, any of which would harm our business, financial condition, results of operations and prospects.

Use of our therapeutic candidates could be associated with side effects, adverse events or other properties or safety risks, which could delay or preclude approval, cause us to suspend or discontinue clinical trials, abandon a therapeutic candidate, limit the commercial profile of an approved label or result in other significant negative consequences that could severely harm our business, prospects, operating results and financial condition.

We have not evaluated any therapeutic candidates in human clinical trials, and we have not yet completed preclinical studies to assess the safety of our lead candidate, ENTR-601-44. Although other oligonucleotide therapeutics, enzyme replacement therapies and gene therapies have received regulatory approval, our EEV-based therapeutics are a novel approach to the delivery of biological therapeutics, which may present enhanced uncertainty associated with the safety profile of ENTR-601-44 and other EEV-based therapeutics compared to more well-established classes of therapies. Moreover, it is impossible to predict when or if any therapeutic candidates we may develop will prove safe in humans. As is the case with biopharmaceuticals generally, it is likely that there may be side effects and adverse events associated with our therapeutic candidates' use. Results of our clinical trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. Undesirable side effects caused by our therapeutic candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or comparable foreign regulatory authorities. The drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

Further, clinical trials by their nature utilize a sample of the potential patient population. With a limited number of patients and limited duration of exposure, rare and severe side effects of our therapeutic candidates may only be uncovered with a significantly larger number of patients exposed to the therapeutic candidate. Any undesirable side effects or unexpected characteristics associated with our therapeutic candidates in clinical trials may lead us to elect to abandon their development or limit their development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective, which may limit the commercial expectations for the therapeutic candidate if approved. We may also be required to modify our study plans based on findings after we commence our clinical trials. Many compounds that initially showed promise in early-stage testing have later been found to cause side effects that prevented further development of the compound. In addition, regulatory authorities may draw different conclusions or require additional testing to confirm these determinations.

It is possible that as we test our therapeutic candidates in larger, longer and more extensive clinical trials, or as the use of these therapeutic candidates becomes more widespread if they receive regulatory approval, illnesses, injuries,

discomforts and other adverse events that were observed in earlier trials, as well as conditions that did not occur or went undetected in previous trials, may be reported by subjects. Any findings of such side effects later in development or upon approval, if any, may harm our business, financial condition and prospects significantly.

Patients treated with our therapeutics, if approved, may experience previously unreported adverse reactions, and it is possible that the FDA or other regulatory authorities may ask for additional safety data as a condition of, or in connection with, our efforts to obtain approval of our therapeutic candidates. If safety problems occur or are identified after our therapeutics, if any, reach the market, we may make the decision or be required by regulatory authorities to amend the labeling of our therapeutics, recall our therapeutics or even withdraw approval for our therapeutics.

Our therapeutic candidates are subject to extensive regulation and compliance, which is costly and time-consuming, and such regulation may cause unanticipated delays or prevent the receipt of the required approvals to commercialize our therapeutic candidates.

The clinical development, manufacturing, labeling, packaging, storage, record-keeping, advertising, promotion, import, export, marketing, distribution and adverse event reporting, including the submission of safety and other information, of our therapeutic candidates are subject to extensive regulation by the FDA in the United States and by comparable foreign regulatory authorities in foreign markets. In the United States, we are not permitted to market our therapeutic candidates until we receive regulatory approval from the FDA. The process of obtaining regulatory approval is expensive, often takes many years following the commencement of clinical trials and can vary substantially based upon the type, complexity and novelty of the therapeutic candidates involved, as well as the target indications and patient population. Approval policies or regulations may change, and the FDA has substantial discretion in the drug approval process, including the ability to delay, limit or deny approval of a therapeutic candidate for many reasons. Despite the time and expense invested in clinical development of therapeutic candidates, regulatory approval is never guaranteed. Neither we nor any current or future collaborator is permitted to market any of our therapeutic candidates in the United States until we receive approval from the FDA.

Prior to obtaining approval to commercialize a therapeutic candidate in the United States or abroad, we or our collaborators must demonstrate with substantial evidence from adequate and well-controlled clinical trials, and to the satisfaction of the FDA or comparable foreign regulatory authorities, that such therapeutic candidates are safe and effective for their intended uses. Results from preclinical studies and clinical trials can be interpreted in different ways. Even if we believe the preclinical or clinical data for our therapeutic candidates are promising, such data may not be sufficient to support approval by the FDA and comparable foreign regulatory authorities. The FDA or comparable foreign regulatory authorities, as the case may be, may also require us to conduct additional preclinical studies or clinical trials for our therapeutic candidates either prior to or post-approval, or may object to elements of our clinical development program.

The FDA or comparable foreign regulatory authorities can delay, limit or deny approval of a therapeutic candidate for many reasons, including:

- such authorities may disagree with the design or implementation of our or our current or future collaborators' clinical trials;
- negative or ambiguous results from our clinical trials or results may not meet the level of statistical significance required by the FDA or comparable foreign regulatory agencies for approval;
- serious and unexpected drug-related side effects may be experienced by participants in our clinical trials or by individuals using drugs similar to our therapeutic candidates;
- such authorities may not accept clinical data from trials which are conducted at clinical facilities or in countries where the standard of care is potentially different from that of the United States;
- we or any of our current or future collaborators may be unable to demonstrate that a therapeutic candidate is safe and effective, and that therapeutic candidate's clinical and other benefits outweigh its safety risks;
- such authorities may disagree with our interpretation of data from preclinical studies or clinical trials;

- such authorities may not agree that the data collected from clinical trials of our therapeutic candidates are acceptable or sufficient to support the submission of an NDA or BLA or other submission or to obtain regulatory approval in the United States or elsewhere, and such authorities may impose requirements for additional preclinical studies or clinical trials;

- such authorities may disagree regarding the formulation, labeling and/or the specifications of our therapeutic candidates;

- approval may be granted only for indications that are significantly more limited than what we apply for and/or with other significant restrictions on distribution and use;

- such authorities may find deficiencies in the manufacturing processes, approval policies or facilities of our third-party manufacturers with which we or any of our current or future collaborators contract for clinical and commercial supplies;

- regulations of such authorities may significantly change in a manner rendering our or any of our potential future collaborators' clinical data insufficient for approval; or

- such authorities may not accept a submission due to, among other reasons, the content or formatting of the submission.

With respect to foreign markets, approval procedures vary among countries and, in addition to the foregoing risks, may involve additional product testing, administrative review periods and agreements with pricing authorities. In addition, events raising questions about the safety of certain marketed biopharmaceuticals may result in increased cautiousness by the FDA and comparable foreign regulatory authorities in reviewing new drugs based on safety, efficacy or other regulatory considerations and may result in significant delays in obtaining regulatory approvals. Any delay in obtaining, or inability to obtain, applicable regulatory approvals would prevent us or any of our potential future collaborators from commercializing our therapeutic candidates.

Our approach to the discovery and development of therapeutic candidates based on our EEV Platform is unproven, and we do not know whether we will be able to develop any products of commercial value, or if competing technological approaches will limit the commercial value of our therapeutic candidates or render our EEV Platform obsolete.

The success of our business depends primarily upon our ability to identify, develop and commercialize products based on our proprietary EEV Platform, which leverages a novel and unproven approach. While we have observed favorable preclinical study results based on our EEV Platform, we have not yet succeeded and may not succeed in demonstrating efficacy and safety for any therapeutic candidates in clinical trials or in obtaining marketing approval thereafter. Our lead therapeutic candidate, ENTR-601-44, is in preclinical development and we have not yet submitted an IND or initiated any clinical trials for any therapeutic candidate. Our research methodology and novel approach to intracellular therapeutics may be unsuccessful in identifying additional therapeutic candidates, and any therapeutic candidates based on our EEV Platform may be shown to have harmful side effects or may have other characteristics that may necessitate additional clinical testing, or make the therapeutic candidates unmarketable or unlikely to receive marketing approval. Further, because all of our therapeutic candidates and development programs are based on our EEV Platform, adverse developments with respect to one of our programs may have a significant adverse impact on the actual or perceived likelihood of success and value of our other programs.

In addition, the biotechnology and biopharmaceutical industries are characterized by rapidly advancing technologies. Our future success will depend in part on our ability to maintain a competitive position with our EEV approach. Failure to stay at the forefront of technological change in utilizing our EEV Platform to create and develop therapeutic candidates may prevent us from competing effectively. Our competitors may render our EEV approach obsolete, or limit the commercial value of our therapeutic candidates, by advances in existing technological approaches or the development of new or different approaches, potentially eliminating the advantages in our drug discovery process that we believe we derive from our research approach and proprietary technologies. By contrast, adverse developments with respect to other companies that attempt to use a similar approach to our approach may adversely impact the actual or perceived value of our EEV Platform and potential of our therapeutic candidates.

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

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

From time to time, we may publicly disclose interim, preliminary or topline data from our preclinical studies and planned clinical trials, which are based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. Topline data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, topline data should be viewed with caution until the final data are available. From time to time, we may also disclose interim, preliminary or topline data from our clinical studies. Interim, topline or preliminary data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Adverse differences between preliminary, topline or interim data and final data could significantly harm our business prospects.

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

We may expend our limited resources to pursue a particular therapeutic candidate or indication, such as our initial focus on developing ENTR-601-44, and fail to capitalize on therapeutic candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited human capital and financial resources, we focus on research programs and therapeutic candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other therapeutic candidates or for other indications that later 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 therapeutic candidates for specific indications may not yield any commercially viable therapeutic candidates. If we do not accurately evaluate the commercial potential or target market for a particular therapeutic candidate, we may relinquish valuable rights to that therapeutic 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 therapeutic candidate.

At any time and for any reason, we may determine that one or more of our discovery programs or pre-clinical or clinical therapeutic candidates or programs does not have sufficient potential to warrant the allocation of resources toward such program or therapeutic candidate. Accordingly, we may choose not to develop a potential therapeutic candidate or elect to suspend, deprioritize or terminate one or more of our discovery programs or pre-clinical or clinical therapeutic candidates or programs. Suspending, deprioritizing or terminating a program or therapeutic candidate in which we have invested significant resources, we will have expended resources on a program that will not provide a full return on our investment and may have missed the opportunity to have allocated those resources to potentially more productive uses, including existing or future programs or therapeutic candidates. For example, in 2020, we made the strategic decision to focus the majority of our immediate efforts on EEV-oligonucleotide opportunities. In order to support ENTR-501 progress, we are exploring partnership opportunities with organizations that have the resources and expertise to continue the development of ENTR-501 into and through clinical development. We continue to believe that the program will have an important role in the future treatment of patients with MNGIE.

We may not be successful in our efforts to expand our development portfolio of therapeutic candidates.

A key element of our strategy is to use our novel EEV Platform to address intracellular targets that are drivers of diseases in genomically defined patient populations with high unmet medical need in order to build a development portfolio of therapeutic candidates. Although our research and development efforts to date have resulted in a development portfolio of potential programs and therapeutic candidates, we may not be able to continue to identify intracellular disease targets and develop therapeutic candidates. We may also pursue opportunities to acquire or in-license additional businesses, technologies or products, form strategic alliances or create joint ventures with third parties to complement or augment our existing business. However, we may not be able to identify any therapeutic candidates for our development portfolio through such acquisition or in-license.

Even if we are successful in continuing to build and expand our development portfolio, the potential therapeutic candidates that we identify may not be suitable for clinical development. For example, they may be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be drugs that will be successful in clinical trials or receive marketing approval and achieve market acceptance. If we do not successfully develop and commercialize therapeutic candidates, we will not be able to obtain drug revenues in future periods, which likely would result in significant harm to our financial position and adversely affect our stock price.

Where appropriate, we plan to secure approval from the FDA, EMA or comparable foreign regulatory authorities through the use of accelerated approval pathways. If we are unable to obtain such approval, we may be required to conduct additional preclinical studies or clinical trials beyond those that we contemplate, which could increase the expense of obtaining, and delay the receipt of, necessary marketing approvals. Even if we receive accelerated approval from the FDA, EMA or comparable regulatory authorities, if our confirmatory trials do not verify clinical benefit, or if we do not comply with rigorous post-marketing requirements, the FDA, EMA or such other regulatory authorities may seek to withdraw accelerated approval.

Where possible, we plan to pursue accelerated development strategies in areas of high unmet need. We may seek an accelerated approval pathway for our one or more of our therapeutic candidates from the FDA, EMA or comparable foreign regulatory authorities. Under the accelerated approval provisions in the Federal Food, Drug, and Cosmetic Act, and the FDA's implementing regulations, the FDA may grant accelerated approval to a therapeutic candidate designed to treat a serious or life-threatening condition that provides meaningful therapeutic benefit over available therapies upon a determination that the therapeutic candidate has an effect on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict clinical benefit. The FDA considers a clinical benefit to be a positive therapeutic effect that is clinically meaningful in the context of a given disease, such as irreversible morbidity or mortality. 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. An intermediate clinical endpoint is a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit. The accelerated approval pathway may be used in cases in which the advantage of a new drug over available therapy may not be a direct therapeutic advantage, but is a clinically important improvement from a patient and public health perspective. If granted, accelerated approval is usually contingent on the sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the drug's clinical benefit. If such post-approval studies fail to confirm the drug's clinical benefit, the FDA may withdraw its approval of the drug.

Prior to seeking accelerated approval, we will seek feedback from the FDA, EMA or comparable foreign regulatory authorities and will otherwise evaluate our ability to seek and receive such accelerated approval. There can be no assurance that after our evaluation of the feedback and other factors we will decide to pursue or submit an NDA or BLA for accelerated approval or any other form of expedited development, review or approval. Similarly, there can be no assurance that after subsequent feedback from the FDA, EMA or comparable foreign regulatory authorities, we will continue to pursue or apply for accelerated approval or any other form of expedited development, review or approval, even if we initially decide to do so. Furthermore, if we decide to submit an application for accelerated approval, there can be no assurance that such application will be accepted or that any approval will be granted on a timely basis, or at all. The FDA, EMA or other comparable foreign regulatory authorities could also require us to conduct further studies prior to considering our application or granting approval of any type, including, for example, if other products are approved via the accelerated pathway and subsequently converted by FDA to full approval. In addition, the FDA currently requires, unless otherwise informed by the agency, pre-approval of promotional materials for products receiving accelerated approval, which could adversely impact the timing of the commercial launch of any of our products. A failure to obtain accelerated approval or

any other form of expedited development, review or approval for our therapeutic candidate would result in a longer time period to commercialization of such therapeutic candidate, could increase the cost of development of such therapeutic candidate and could harm our competitive position in the marketplace.

We may seek Fast Track designation, Breakthrough Therapy designation and/or orphan drug designation from the FDA or similar designations from other regulatory authorities for one or more of our therapeutic candidates. Even if one or more of our therapeutic candidates receive any of these designations, we may be unable to obtain or maintain the benefits associated with such designation.

The FDA has established various designations to facilitate more rapid and efficient development and approval of certain types of drugs. Such designations include Fast Track designation, Breakthrough Therapy designation, and orphan drug designation. Fast Track designation is designed to facilitate the development and expedite the review of therapies for serious conditions that fill an unmet medical need. Programs with Fast Track designation may benefit from early and frequent communications with the FDA, potential priority review and the ability to submit a rolling application for regulatory review. Fast Track designation applies to both the therapeutic candidate and the specific indication for which it is being studied. If any of our therapeutic candidates receive Fast Track designation but do not continue to meet the criteria for Fast Track designation, or if our clinical trials are delayed, suspended or terminated, or put on clinical hold due to unexpected adverse events or issues with clinical supply, we will not receive the benefits associated with the Fast Track program. Fast Track designation alone does not guarantee qualification for the FDA's priority review procedures.

A Breakthrough Therapy, on the other hand, 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. For therapeutic candidates that have been designated as Breakthrough Therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Designation as a Breakthrough Therapy is within the discretion of the FDA, and drugs designated as Breakthrough Therapies by the FDA may also be eligible for other expedited approval programs, including accelerated approval. Even if one or more of our therapeutic candidates qualify as Breakthrough Therapies pursuant to FDA standards, the FDA may later decide that the product no longer meets the conditions for qualification. Thus, even though we may seek Breakthrough Therapy designation for one or more of our current or future therapeutic candidates, there can be no assurance that we will receive Breakthrough Therapy designation.

Regulatory authorities in some jurisdictions, including the United States and the EU, may also designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a therapeutic candidate as an orphan drug if it is a drug intended to treat a rare condition, which is generally defined as a patient population of fewer than 200,000 individuals annually in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the EU, the EMA's Committee for Orphan Medicinal Products (COMP) evaluates orphan designation to promote the development of products that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting no more than five (5) in ten thousand (10,000) persons in the EU, or where the product, without the benefits derived from orphan status, would not generate sufficient return in the EU to justify the necessary investment in its development. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers, and it may entitle the therapeutic to exclusivity in the United States and the EU. Even if we obtain orphan drug designation for a therapeutic candidate, we may not be able to obtain or maintain orphan drug exclusivity for that therapeutic candidate.

If any of our programs or therapeutic candidates receive Fast Track, Breakthrough Therapy or orphan drug designation by the FDA or similar designations by other regulatory authorities, there is no assurance that we will receive any benefits from such programs or that we will continue to meet the criteria to maintain such designation. Even if we obtain such designations, we may not experience a faster development process, review or approval compared to conventional FDA procedures. A Fast Track, Breakthrough Therapy, or orphan drug designation does not ensure that a therapeutic candidate will receive marketing approval or that approval will be granted within any particular timeframe.

Obtaining and maintaining marketing approval or commercialization of our therapeutic candidates in the United States does not mean that we will be successful in obtaining marketing approval of our therapeutic candidates in other jurisdictions. Failure to obtain marketing approval in foreign jurisdictions would prevent any therapeutic candidates we may develop from being marketed in such jurisdictions, which, in turn, would materially impair our ability to generate revenue.

In order to market and sell any therapeutic candidates we may develop in the EU and many other foreign jurisdictions, we or our collaborators must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We or these third parties may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. We may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our medicines in any jurisdiction, which would materially impair our ability to generate revenue.

Additionally, we could face heightened risks with respect to seeking marketing approval in the United Kingdom as a result of the withdrawal of the United Kingdom from the EU, commonly referred to as Brexit. On December 24, 2020, the United Kingdom and the EU entered into a Trade and Cooperation Agreement, which became provisionally applicable on January 1, 2021 and has been formally applicable since May 1, 2021. This agreement is comprehensive and provides some details on how aspects of the United Kingdom and EU's relationship regarding medicinal products will operate, particularly in relation to Good Manufacturing Practice, however it does not foresee wholesale mutual recognition of UK and EU pharmaceutical regulations. Great Britain is therefore no longer covered by the centralized procedure for obtaining EU-wide marketing authorizations from the EMA for medicinal products (under the Northern Ireland Protocol, the EU regulatory framework will continue to apply in Northern Ireland and centralized EU authorizations will continue to be recognized) and a separate process for authorization of drug products will be required in Great Britain. For a period of two years from January 1, 2021, the Medicines and Healthcare Products Regulatory Agency may rely on a decision taken by the European Commission on the approval of a new marketing authorization in the centralized procedure, in order to more quickly grant a new Great Britain marketing authorization, however a separate application will still be required.

Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of the Trade and Cooperation Agreement or otherwise, would prevent us from commercializing any therapeutic candidates in the United Kingdom and/or the EU and restrict our ability to generate revenue and achieve or sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or the EU for any therapeutic candidates that we may develop, which could significantly and materially harm our business.

The FDA, EMA and other comparable foreign regulatory authorities may not accept data from trials conducted in locations outside of their jurisdiction.

We anticipate we will initially conduct clinical trials of our therapeutic candidates in the United States and we may choose to conduct our clinical trials internationally as well. The acceptance of study data by the FDA, EMA or other comparable foreign regulatory authority from clinical trials conducted outside of their respective jurisdictions may be subject to certain conditions. In cases where data from United States clinical trials are intended to serve as the basis for marketing approval in the foreign countries outside the United States, the standards for clinical trials and approval may be different. There can be no assurance that any United States or foreign regulatory authority would accept data from trials conducted outside of its applicable jurisdiction. If the FDA, EMA or any applicable foreign regulatory authority does not accept such data, it would result in the need for additional trials, which would be costly and time-consuming and delay aspects of our business plan, and which may result in our therapeutic candidates not receiving approval or clearance for commercialization in the applicable jurisdiction.

Changes in methods of therapeutic candidate manufacturing or formulation may result in additional costs or delay, which could adversely affect our business, results of operations and financial condition.

As therapeutic candidates progress through preclinical and clinical trials to marketing approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods and formulation, are altered along the way in an effort to optimize yield and manufacturing batch size, minimize costs and achieve consistent quality and results. For example, we may introduce an alternative formulation of one or more of our therapeutic candidates during the course of our planned clinical trials. Such changes carry the risk that they will not achieve these intended objectives. Any of these changes could cause our therapeutic candidates to perform differently and affect the results of planned clinical trials or other future clinical trials conducted with the altered materials. This could delay completion of clinical trials, require the conduct of bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our therapeutic candidates and jeopardize our ability to commercialize our therapeutic candidates, if approved, and generate revenue.

Even if we, or any collaborators we may have, obtain marketing approvals for any therapeutic candidates we may develop, the terms of approvals and ongoing regulation of our therapeutics could require the substantial expenditure of resources and may limit how we, or they, manufacture and market our therapeutics, which could materially impair our ability to generate revenue.

Any therapeutic candidate for which we obtain marketing approval, if ever, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such medicine, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to quality control, quality assurance and corresponding maintenance of records and documents, compliance with applicable product tracking and tracing requirements, and requirements regarding the distribution of samples to physicians and recordkeeping. For example, the holder of an approved BLA is obligated to monitor and report adverse events and any failure of a product to meet the specifications in the BLA. The FDA typically advises that patients treated with genetic medicine undergo follow-up observations for potential adverse events for a 15-year period. The holder of an approved BLA must also submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Even if marketing approval of a therapeutic candidate is granted, the approval may be subject to limitations on the indicated uses for which the medicine may be marketed or to the conditions of approval, or contain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the medicine.

Accordingly, assuming we, or any third parties we may collaborate with, receive marketing approval for one or more therapeutic candidates we may develop, we, and such collaborators, and our and their contract manufacturers will continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance and quality control. If we and such collaborators are not able to comply with post-approval regulatory requirements, we and such collaborators could have the marketing approvals for our therapeutics withdrawn by regulatory authorities and our, or such collaborators', ability to market any future products could be limited, which could adversely affect our ability to achieve or sustain profitability. Further, the cost of compliance with post-approval regulations may have a negative effect on our business, operating results, financial condition and prospects.

If we fail to comply with applicable regulatory requirements following approval of any therapeutic candidates we may develop, a regulatory agency may:

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve a pending BLA or supplements to a BLA submitted by us;
- seize product; or

- refuse to allow us to enter into supply contracts, including government contracts.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize any therapeutic candidates we may develop and generate revenues.

Clinical trial and product liability lawsuits against us could divert our resources, could cause us to incur substantial liabilities and could limit commercialization of any therapeutic candidates we may develop.

We will face an inherent risk of clinical trial and product liability exposure related to the testing of any therapeutic candidates we may develop in clinical trials, and we will face an even greater risk if we commercially sell any products that we may develop. While we currently have no therapeutic candidates in clinical trials or that have been approved for commercial sale, the future use of therapeutic candidates by us in clinical trials, and the sale of any approved products in the future, may expose us to liability claims. These claims might be made by patients that use the product, healthcare providers, pharmaceutical companies or others selling such products. If we cannot successfully defend ourselves against claims that our therapeutic candidates or products caused injuries, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any therapeutic candidates we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants and inability to continue clinical trials;
- initiation of investigations by regulators;
- significant costs to defend any related litigation;
- substantial monetary awards to trial participants or patients;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- loss of revenue;
- exhaustion of any available insurance and our capital resources;
- decline in our stock price;
- reduced resources of our management to pursue our business strategy; and
- the inability to commercialize any therapeutic candidates we may develop.

We will need to increase our insurance coverage if we commence clinical trials or if we commence commercialization of any therapeutic candidates. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise. If and when coverage is secured, our insurance policies may also have various exclusions and we may be subject to a product liability claim for which we have no coverage. Even if our agreements with any future corporate collaborators entitle us to indemnification against losses, such indemnification may not be available or adequate should any claim arise. If a successful clinical trial or product liability claim or series of claims is brought against us for uninsured liabilities or in excess of insured liabilities, our assets may not be sufficient to cover such claims and our business operations could be impaired.

We may develop our current or future therapeutic candidates in combination with other therapies, which would expose us to additional risks.

We may develop our current or potential future therapeutic candidates in combination with one or more currently approved therapies or therapies in development. Even if any of our current or future therapeutic candidates were to receive marketing approval or be commercialized for use in combination with other existing therapies, we would continue to be subject to the risks that the FDA, EMA or other comparable foreign regulatory authorities could revoke approval of the therapy used in combination with any of our therapeutic candidates, or safety, efficacy, manufacturing or supply issues could arise with these existing therapies. In addition, it is possible that existing therapies with which our therapeutic candidates are approved for use could themselves fall out of favor or be relegated to later lines of treatment. This could result in the need to identify other combination therapies for our therapeutic candidates or our own products being removed from the market or being less successful commercially.

We may also evaluate our current or future therapeutic candidates in combination with one or more other therapies that have not yet been approved for marketing by the FDA, EMA or comparable foreign regulatory authorities. We will not be able to market and sell any therapeutic candidate in combination with any such unapproved therapies that do not ultimately obtain marketing approval.

Furthermore, we cannot be certain that we will be able to obtain a steady supply of such therapies for use in developing combinations with our therapeutic candidates on commercially reasonable terms or at all. Any failure to obtain such therapies for use in clinical development and the expense of purchasing therapies in the market may delay our development timelines, increase our costs and jeopardize our ability to develop our therapeutic candidates as commercially viable therapies. If the FDA, EMA or other comparable foreign regulatory authorities do not approve or withdraw their approval of these other therapies, or if safety, efficacy, commercial adoption, manufacturing or supply issues arise with the therapies we choose to evaluate in combination with any of our current or future therapeutic candidates, we may be unable to obtain approval of or successfully market any one or all of the current or future therapeutic candidates we develop. Additionally, if the third-party providers of therapies or therapies in development used in combination with our current or future therapeutic candidates are unable to produce sufficient quantities for clinical trials or for commercialization of our current or future therapeutic candidates, or if the cost of combination therapies are prohibitive, our development and commercialization efforts would be impaired, which would have an adverse effect on our business, financial condition, results of operations and growth prospects.

Risks Related to Our Reliance on Third Parties

We rely, and expect to continue to rely, on third parties to conduct some or all aspects of our product manufacturing, research and preclinical and clinical testing, and these third parties may not perform satisfactorily.

We do not expect to independently conduct all aspects of our product manufacturing, research and preclinical and clinical testing. We currently rely, and expect to continue to rely, on third parties with respect to many of these items, including contract manufacturing organizations (CMOs) for the manufacturing of any therapeutic candidates we test in preclinical or clinical development, as well as CROs for the conduct of our animal testing and research and CROs for the conduct of our planned clinical trials. Any of these third parties may terminate their engagements with us at any time. A need to enter into alternative arrangements could delay our product development activities, and we may not be able to enter into alternative arrangements on reasonable terms, if at all.

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 responsibility to ensure compliance with all required regulations and study protocols. For example, for therapeutic candidates that we develop and commercialize on our own, we will remain responsible for ensuring that each of our IND-enabling studies and clinical trials are conducted in accordance with the study plan and protocols. Moreover, the FDA requires us to comply with cGCPs for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. We also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, clinicaltrials.gov, within specified timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions. If we or any of our CROs or other third parties, including trial sites, fail to comply with applicable cGCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, EMA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure our stockholders that upon inspection by a given

regulatory authority, such regulatory authority will determine that any of our clinical trials complies with cGCP regulations. In addition, our clinical trials must be conducted with product produced under conditions that comply with the FDA's current Good Manufacturing Practices. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process.

Although we intend to design the clinical trials for any therapeutic candidates we may develop, CROs will conduct some or all of the clinical trials. As a result, many important aspects of our development programs, including their conduct and timing, will be outside of our direct control. Our reliance on third parties to conduct future preclinical studies and clinical trials will also result in less direct control over the management of data developed through preclinical studies and clinical trials than would be the case if we were relying entirely upon our own staff. Communicating with outside parties can also be challenging, potentially leading to mistakes as well as difficulties in coordinating activities. Outside parties may:

- have staffing difficulties;
- be unable to acquire the necessary supplies to perform successfully;
- fail to comply with contractual obligations;
- experience regulatory compliance issues;
- undergo changes in priorities or become financially distressed; or
- form relationships with other entities, some of which may be our competitors.

These factors may materially adversely affect the willingness or ability of third parties to conduct our preclinical studies and clinical trials and may subject us to unexpected cost increases that are beyond our control. We expect to have to negotiate budgets and contracts with CROs and trial sites, which may result in delays to our development timelines and increased costs. In addition, any third parties conducting our clinical trials will not be our employees, and except for remedies available to us under our agreements with such third parties, we cannot control whether or not they devote sufficient time and resources to our clinical programs. If these CROs, and any other third parties we engage do not perform preclinical studies and future clinical trials in a satisfactory manner, if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, or if they breach their obligations to us or fail to comply with regulatory requirements, the development, regulatory approval and commercialization of any therapeutic candidates we may develop may be delayed, we may not be able to obtain regulatory approval and commercialize our therapeutic candidates or our development programs may be materially and irreversibly harmed. If we are unable to rely on preclinical and clinical data collected by our CROs and other third parties, we could be required to repeat, extend the duration of or increase the size of any preclinical studies or clinical trials we conduct and this could significantly delay commercialization and require greater expenditures.

Nevertheless, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, legal and regulatory requirements and scientific standards and our reliance on third parties does not relieve us of our regulatory responsibilities. We and these third parties are required to comply with GCP requirements, which are regulations and guidelines enforced by the FDA and other regulatory authorities for therapeutic candidates in clinical development. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, clinical investigators and trial sites. If we or any of these third parties fail to comply with applicable GCP requirements, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or other regulatory authorities may require us to suspend, place on clinical hold or terminate these trials or perform additional preclinical studies or clinical trials before approving our marketing applications. We cannot be certain that, upon inspection, such regulatory authorities will determine that any of our clinical trials comply with the GCP requirements. In addition, our clinical trials must be conducted with biologic product produced under cGMP requirements and may require a large number of patients. In the U.S., we also are required to register ongoing clinical trials and post the results of completed clinical trials on a government-sponsored database, clinicaltrials.gov, within certain timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

These third parties may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other product development activities, which could affect their performance on our behalf. If these third parties do not successfully carry out their contractual duties or obligations or meet

expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to complete development of, obtain regulatory approval of or successfully commercialize our therapeutic candidates. As a result, our financial results and the commercial prospects for our therapeutic candidates would be harmed, our costs could increase and our ability to generate revenue could be delayed.

Our failure or any failure by these third parties to comply with these regulations or to recruit a sufficient number of patients may require us to repeat clinical trials, which would delay the regulatory approval process. Moreover, our business may be implicated if any of these third parties violates federal or state fraud and abuse or false claims laws and regulations or healthcare privacy and security laws. For any violations of laws and regulations during the conduct of our preclinical studies and clinical trials, we could be subject to warning letters or enforcement action that may include civil penalties up to and including criminal prosecution.

If any of our relationships with these third-party CROs or others terminate, we may not be able to enter into arrangements with alternative CROs or other third parties or to do so on commercially reasonable terms. Switching or adding additional CROs involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO begins work. As a result, delays may occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects. If 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 preclinical studies and clinical trials required to support future IND submissions and approval of any therapeutic candidates we may develop.

We are dependent on third-party vendors to provide certain licenses, products and services and our business and operations, including clinical trials, could be disrupted by any problems with our significant third-party vendors.

We engage a number of third-party suppliers and service providers to supply critical goods and services, such as contract research services, contract manufacturing services and IT services. Disruptions to the business, financial stability or operations of these suppliers and service providers, including due to strikes, labor disputes or other disruptions to the workforce, for instance, if, as a result of the ongoing COVID-19 pandemic, employees are not able to come to work, or to their willingness and ability to produce or deliver such products or provide such services in a manner that satisfies the requirements put forth by the authorities, or in a manner that satisfies our own requirements, could affect our ability to develop and market our future therapeutic candidates on a timely basis. If these suppliers and service providers were unable or unwilling to continue to provide their products or services in the manner expected, or at all, we could encounter difficulty finding alternative suppliers. Even if we are able to secure appropriate alternative suppliers in a timely manner, costs for such products or services could increase significantly. Additionally, since the beginning of the pandemic, three vaccines for COVID-19 were granted Emergency Use Authorization by the FDA, and two of those later received marketing approval. Additional vaccines may be authorized in the future. The resultant demand for vaccines and potential for manufacturing facilities and materials to be commandeered under the Defense Production Act of 1950, or equivalent foreign legislation, may make it more difficult to obtain materials or manufacturing slots for the products needed for our clinical trials, which could lead to delays in these trials. Any of these events could adversely affect our results of operations and our business.

Our EEV-based therapeutic candidates are based on novel technologies and any therapeutic candidates we develop may be complex and difficult to manufacture. We may encounter difficulties in manufacturing, product release, shelf life, testing, storage, supply chain management or shipping. If we or any of our third-party manufacturers encounter such difficulties, our ability to supply material for clinical trials or any approved product could be delayed or stopped.

The manufacturing processes for our therapeutic candidates are novel. There are no medicines incorporating or utilizing our EEV Platform that have been commercialized to date or manufactured at such scale. Due to the novel nature of this technology and limited experience at larger scale production, we may encounter difficulties in manufacturing, product release, shelf life, testing, storage and supply chain management, or shipping. These difficulties could be due to any number of reasons including, but not limited to, complexities of producing batches at larger scale, equipment failure, choice and quality of raw materials and excipients, analytical testing technology, and product instability. In an effort to optimize product features, we have in the past and may in the future make changes to our therapeutic candidates in their manufacturing and stability formulation and conditions. This has in the past resulted in and may in the future result in our

having to resupply batches for preclinical or clinical activities when there is insufficient product stability during storage and insufficient supply. Insufficient stability or shelf life of our therapeutic candidates could materially delay our or our strategic collaborators' ability to continue the clinical trial for that therapeutic candidate or require us to begin a new clinical trial with a newly formulated drug product, due to the need to manufacture additional preclinical or clinical supply.

Our rate of innovation is high, which has resulted in and will continue to cause a high degree of technology change that can negatively impact product comparability during and after clinical development. Furthermore, technology changes may drive the need for changes in, modification to, or the sourcing of new manufacturing infrastructure or may adversely affect third-party relationships.

The process to generate our EEV-based therapeutics is complex and, if not developed and manufactured under well-controlled conditions, can adversely impact pharmacological activity. Furthermore, we have not manufactured our EEV-based therapeutics at commercial scale. We may encounter difficulties in scaling up our manufacturing process, thereby potentially impacting clinical and commercial supply.

During clinical development of our EEV-based therapeutics, in many cases, we may have to utilize multiple batches of drug substance and drug product to meet the clinical supply requirement of a single clinical trial. Failure in our ability to scale up batch size or failure in any batch may lead to a substantial delay in our clinical trials.

As we continue developing new manufacturing processes for our drug substance and drug product, the changes we implement to manufacturing process may in turn impact specification and stability of the drug product. Changes in our manufacturing processes may lead to failure of lots and this could lead to a substantial delay in our clinical trials. Our EEV-based therapeutic candidates may prove to have a stability profile that leads to a lower than desired shelf life of our final approved EEV-based product. This poses risk in supply requirements, wasted stock, and higher cost of goods.

Due to the number of different programs, we may have cross contamination of products inside of our factories, CROs, suppliers, or in the clinic that affect the integrity of our therapeutics.

As we scale the manufacturing output for particular programs, we plan to continuously improve yield, purity, and the pharmaceutical properties of our development candidates from IND-enabling studies through commercial launch, including shelf life stability, and solubility properties of drug product and drug substance. Because of continuous improvement in manufacturing processes, we may switch processes for a particular program during development. However, after the change in process, more time is required for pharmaceutical property testing, such as 6 or 12 month stability testing. That may require resupplying clinical material, or making additional cGMP batches to keep up with clinical trial demand before such pharmaceutical property testing is completed.

We are utilizing a number of raw materials and excipients that are either new to the pharmaceutical industry or are being employed in a novel manner. Some of these raw materials and excipients have not been scaled to a level to support commercial supply and could experience unexpected manufacturing or testing failures, or supply shortages. Such issues with raw materials and excipients could cause delays or interruptions to clinical and commercial supply of our therapeutic candidates. Further, now and in the future one or more of our programs may have a single source of supply for raw materials and excipients.

We may establish a number of analytical assays to assess the quality of our EEV-based therapeutic candidates. We may identify gaps in our analytical testing strategy that might prevent release of product or could require product withdrawal or recall. For example, we may discover new impurities that have an impact on product safety, efficacy, or stability. This may lead to an inability to release our therapeutic candidates until the manufacturing or testing process is rectified.

We may find that our therapeutic candidates are extremely temperature sensitive, and we may learn that any or all of our therapeutics are less stable than desired. We may also find that transportation conditions negatively impact product quality. This may require changes to the formulation or manufacturing process for one or more of our therapeutic candidates and result in delays or interruptions to clinical or commercial supply. In addition, the cost associated with such transportation services and the limited pool of vendors may also add additional risks of supply disruptions.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we currently rely on third parties to manufacture our therapeutic candidates and to perform quality testing, we must, at times, share our proprietary technology and confidential information, including trade secrets, with them. We seek to protect our proprietary technology, in part, by entering into confidentiality agreements, and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with our collaborators, advisors, employees and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are intentionally or inadvertently incorporated into the technology of others or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets and despite our efforts to protect our trade secrets, a competitor's discovery of our proprietary technology and confidential information or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business, financial condition, results of operations and prospects.

We may from time to time be dependent on single-source suppliers for some of the components and materials used in the therapeutic candidates we may develop.

We may from time to time depend on single-source suppliers for some of the components and materials used in any therapeutic candidates we may develop. We cannot ensure that these suppliers or service providers will remain in business, have sufficient capacity or supply to meet our needs or that they will not be purchased by one of our competitors or another company that is not interested in continuing to work with us. Our use of single-source suppliers of raw materials, components, key processes and finished goods could expose us to several risks, including disruptions in supply, price increases or late deliveries. There are, in general, relatively few alternative sources of supply for substitute components. These vendors may be unable or unwilling to meet our future demands for our clinical trials or commercial sale. Establishing additional or replacement suppliers for these components, materials and processes could take a substantial amount of time and it may be difficult to establish replacement suppliers who meet regulatory requirements. Any disruption in supply from any single-source supplier or service provider could lead to supply delays or interruptions which would damage our business, financial condition, results of operations and prospects.

If we have to switch to a replacement supplier, the manufacture and delivery of any therapeutic candidates we may develop could be interrupted for an extended period, which could adversely affect our business. Establishing additional or replacement suppliers, if required, may not be accomplished quickly. If we are able to find a replacement supplier, the replacement supplier would need to be qualified and may require additional regulatory authority approval, which could result in further delay. While we seek to maintain adequate inventory of the single source components and materials used in our therapeutics, any interruption or delay in the supply of components or materials, or our inability to obtain components or materials from alternate sources at acceptable prices in a timely manner, could impair our ability to meet the demand for our investigational medicines.

We may enter into collaborations, licenses and other similar arrangements with third parties for the research, development and commercialization of certain of the therapeutic candidates we may develop. If any such arrangements are not successful, we may not be able to capitalize on the market potential of those therapeutic candidates.

We may seek third-party collaborators for the research, development and commercialization of certain of the therapeutic candidates we may develop. If we enter into any such arrangements with any third parties, we will likely have limited control over the amount and timing of resources that our partners dedicate to the development or commercialization of any therapeutic candidates we may seek to develop with them. Our ability to generate revenues from these arrangements will depend on our abilities to successfully perform the functions assigned to them in these arrangements. We cannot predict the success of any arrangement that we enter into.

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

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

- collaborators may not perform their obligations as expected;
- collaborators may not pursue development and commercialization of any therapeutic candidates we may develop or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborator's strategic focus or available funding or external factors such as an acquisition that diverts resources or creates competing priorities;
- collaborators may delay programs, preclinical studies or clinical trials, provide insufficient funding for programs, preclinical studies or clinical trials, stop a preclinical study or clinical trial or abandon a therapeutic candidate, repeat or conduct new clinical trials or require a new formulation of a therapeutic candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with any therapeutic candidates we may develop if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- collaborators may be acquired by a third party having competitive products or different priorities, causing the emphasis on our product development or commercialization program under such collaboration to be delayed, diminished or terminated;
- collaborators 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 obtain, maintain, enforce or defend our intellectual property or proprietary 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;
- if a collaborator of ours is involved in a business combination, the collaborator might deemphasize or terminate the development or commercialization of any therapeutic candidate licensed to it by us;
- our collaborators' business or operations could be disrupted due to the ongoing COVID-19 pandemic or other reasons outside of our control, which could have an adverse impact on their development and commercialization efforts or the prospects of our collaboration;
- disputes may arise between the collaborators and us that result in the delay or termination of the research, development, or commercialization of any therapeutic candidates we may develop or that result in costly litigation or arbitration that diverts management attention and resources;
- we may lose certain valuable rights under certain circumstances, including if we undergo a change of control;
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable therapeutic candidates we may develop; and
- collaboration agreements may not lead to development or commercialization of therapeutic candidates in the most efficient manner or at all.

If our collaborations do not result in the successful development and commercialization of therapeutic candidates, or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of therapeutic candidates could be delayed, and we may need additional resources to develop therapeutic candidates. In addition, if one of our collaborators terminates its agreement with us, we may find it more difficult to find a suitable replacement collaborator or attract new collaborators, and our development programs may be delayed or the perception of us in the business and financial communities could be adversely affected. All of the risks relating to product development, regulatory approval and commercialization described in this Annual Report apply to the activities of our collaborators.

These relationships, or those like them, may require us to incur non-recurring and other charges, increase our near- and long-term expenditures, issue securities that dilute our existing stockholders, or disrupt our management and business. In addition, we could face significant competition in seeking appropriate collaborators, and the negotiation process is time-consuming and complex. Our ability to reach a definitive collaboration agreement will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration, and the proposed collaborator's evaluation of several factors. If we license rights to any therapeutic candidates we or our collaborators may develop, we may not be able to realize the benefit of such transactions if we are unable to successfully integrate them with our existing operations and company culture.

If conflicts arise between us and our potential collaborators, these parties may act in a manner adverse to us and could limit our ability to implement our strategies.

If conflicts arise between us and our potential collaborators, the other party may act in a manner adverse to us and could limit our ability to implement our strategies. Our collaborators may develop, either alone or with others, products in related fields that are competitive with the therapeutic candidates we may develop that are the subject of these collaborations with us. Competing products, either developed by the collaborators or to which the collaborators have rights, may result in the withdrawal of support for our therapeutic candidates.

Some of our future collaborators could also become our competitors. Our collaborators could develop competing products, preclude us from entering into collaborations with their competitors, fail to obtain timely regulatory approvals, terminate their agreements with us prematurely, fail to devote sufficient resources to the development and commercialization of products, or merge with or be acquired by a third party who may do any of these things. Any of these developments could harm our product development efforts.

If we are not able to establish collaborations on commercially reasonable terms, we may have to alter our development and commercialization plans.

Our product development and research programs and the potential commercialization of any therapeutic candidates we may develop will require substantial additional cash to fund expenses. For some of the therapeutic candidates we may develop, we may decide to collaborate with other pharmaceutical and biotechnology companies for the development and potential commercialization of those therapeutic candidates.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration, and the proposed collaborator's evaluation of a number of factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA, the EMA or similar regulatory authorities outside the United States, the potential market for the subject therapeutic candidate, the costs and complexities of manufacturing and delivering such therapeutic candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge, and industry and market conditions generally. The collaborator may also consider alternative therapeutic candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us.

Collaborations are complex and time-consuming to negotiate and document. 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.

We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of the therapeutic candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization, reduce the scope of any sales or marketing activities, or increase our own expenditures on the development of the therapeutic candidate.

Risks Related to Commercialization of Our Therapeutic Candidates

The commercial success of our therapeutic candidates will depend upon the degree of market acceptance of such therapeutic candidates by physicians, patients, healthcare payors and others in the medical community.

Our therapeutic candidates may not be commercially successful. Even if any of our therapeutic candidates receive regulatory approval, they may not gain market acceptance among physicians, patients, healthcare payors or the medical community. The commercial success of any of our current or future therapeutic candidates will depend significantly on the broad adoption and use of the resulting product by physicians and patients for approved indications. The degree of market acceptance of our therapeutics will depend on a number of factors, including:

- demonstration of clinical efficacy and safety compared to other more-established products;
- the indications for which our therapeutic candidates are approved;
- the limitation of our targeted patient population and other limitations or warnings contained in any FDA-approved labeling;
- acceptance of a new drug for the relevant indication by healthcare providers and their patients;
- the pricing and cost-effectiveness of our therapeutics, as well as the cost of treatment with our therapeutics in relation to alternative treatments and therapies;
- our ability to obtain and maintain sufficient third-party coverage and adequate reimbursement from government healthcare programs, including Medicare and Medicaid, private health insurers and other third-party payors;
- the willingness of patients to pay all, or a portion of, out-of-pocket costs associated with our therapeutics in the absence of sufficient third-party coverage and adequate reimbursement;
- any restrictions on the use of our therapeutics, and the prevalence and severity of any adverse effects;
- potential product liability claims;
- the timing of market introduction of our therapeutics as well as competitive drugs;
- the effectiveness of our or any of our current or potential future collaborators' sales and marketing strategies; and
- unfavorable publicity relating to the product.

If any therapeutic candidate is approved but does not achieve an adequate level of acceptance by physicians, hospitals, healthcare payors or patients, we may not generate sufficient revenue from that product and may not become or remain profitable. Our efforts to educate the medical community and third-party payors regarding the benefits of our therapeutics may require significant resources and may never be successful.

Even if we are able to commercialize any of our therapeutic candidates, if approved, such therapeutic candidate may become subject to unfavorable pricing regulations or third-party coverage and reimbursement policies, which would harm our business.

The regulations that govern regulatory approvals, pricing and reimbursement for new products vary widely from country to country. Some countries require approval of the sale price of a product before it can be marketed. In many countries, the pricing review period begins after marketing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a therapeutic candidate in a particular country, but then be subject to price regulations that delay our commercial launch of the therapeutic candidate, possibly for lengthy time periods, and negatively

impact the revenues we are able to generate from the sale of the therapeutic candidate in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more therapeutic candidates, even if our therapeutic candidates obtain marketing approval.

Our ability to commercialize any therapeutic candidates successfully also will depend in part on the extent to which coverage and reimbursement for these therapeutic candidates and related treatments will be available from government authorities, private health insurers and other organizations. In the U.S. and markets in other countries, patients generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. Adequate coverage and reimbursement from governmental healthcare programs, such as Medicare and Medicaid, and commercial payors is critical to new product acceptance.

In the United States, the principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services (CMS), an agency within the U.S. Department of Health and Human Services (HHS). CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare and private payors tend to follow CMS to a substantial degree. The availability of coverage and extent of reimbursement by governmental and private payors is essential for most patients to be able to afford treatments. Sales of these or other products that we may identify will depend substantially, both domestically and abroad, on the extent to which the costs of our therapeutics will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other third-party payors. If coverage and adequate reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize our therapeutics. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment. Factors payors consider in determining reimbursement are based on whether the product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular products. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for products. We cannot be sure that coverage will be available for any therapeutic candidate that we commercialize and, if coverage is available, the level of reimbursement.

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. Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. We cannot be sure that reimbursement will be available for any therapeutic candidate that we commercialize and, if reimbursement is available, the level of reimbursement. In addition, many pharmaceutical manufacturers must calculate and report certain price reporting metrics to the government, such as average sales price (ASP) and best price. Penalties may apply in some cases when such metrics are not submitted accurately and timely. Further, these prices for drugs may be reduced by mandatory discounts or rebates required by government healthcare programs.

In addition, in some foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the EU provides options for its Member States to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost effectiveness of a particular therapeutic candidate to currently available therapies. A Member State may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing

the medicinal product on the market. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our therapeutic candidates. Historically, products launched in the EU do not follow price structures of the U.S. and generally prices tend to be significantly lower.

We face significant competition, and if our competitors develop technologies or therapeutic candidates more rapidly than we do or their technologies are more effective, our business and our ability to develop and successfully commercialize products may be adversely affected.

The biotechnology and biopharmaceutical industries are characterized by rapid advancing technologies, intense competition and a strong emphasis on proprietary and novel products and therapeutic candidates. Our competitors have developed, are developing or may develop products, therapeutic candidates and processes competitive with our therapeutic candidates. Any therapeutic candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future. We believe that a significant number of products are currently under development, and may become commercially available in the future, for the treatment of conditions for which we may attempt to develop therapeutic candidates. Our competitors include larger and better funded pharmaceutical, biopharmaceutical, biotechnological and therapeutics companies. Moreover, we may also compete with universities and other research institutions who may be active in the indications we are targeting and could be in direct competition with us. We also compete with these organizations to recruit management, scientists and clinical development personnel, which could negatively affect our level of expertise and our ability to execute our business plan. We will also face competition in establishing clinical trial sites, enrolling subjects for clinical trials and in identifying and in-licensing new therapeutic candidates. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

Currently, patients with DMD are treated with corticosteroids to manage the inflammatory component of the disease. EMFLAZA (deflazacort) is an FDA-approved corticosteroid marketed by PTC Therapeutics, Inc. (PTC). In addition, there are four FDA-approved exon skipping drugs: EXONDYS 51 (eteplirsen), VYONDYS 53 (golodirsen), and AMONDYS 45 (casimersen), which are PMOs approved for the treatment of patients with DMD who are amenable to exon 51, exon 53 and exon 45 skipping, respectively, and are marketed by Sarepta Therapeutics, Inc. (Sarepta), and VILTEPSO (vitolarsen), a PMO approved for the treatment of patients with DMD who are amenable to exon 53 skipping, which is marketed by Nippon Shinyaku Co. Ltd. Companies focused on developing treatments for DMD that target dystrophin mechanisms, as does our DMD program, include Sarepta with SRP-5051, a peptide-linked PMO currently being evaluated following a Phase 2 clinical trial for patients amenable to exon 51 skipping along with SRP-5053,SRP-5045 and SRP-5044 in preclinical development, PTC with ataluren, a small molecule targeting nonsense mutations in a Phase 3 clinical trial, Avidity Biosciences, Inc. (Avidity), which is in preclinical development with an antibody oligonucleotide conjugate for exons 44 (AOC-1044), 45 and 51 that targets dystrophin production, Wave Life Sciences Ltd., which is clinically evaluating WVE-N531, a splicing candidate that is designed to target exon 53 within the dystrophin gene, Dyne Therapeutics, Inc. (Dyne), which is pursuing antibody fragment-oligonucleotide conjugates for exons 44, 45, 51 (DYNE-251), and 53, PepGen, Inc. with PGN-EDO51, a preclinical candidate designed to address exon 51, and BioMarin Pharmaceutical Inc., which is in preclinical development with BMN 351, an antisense oligonucleotide therapy for exon 51. In addition, several companies are developing gene therapies to treat DMD, including Audentes Therapeutics, Inc. (AT466 AAV antisense exon 2 skipping candidate, and AT751 and AT753, AAV-antisense exon 51 and 53 skipping candidates, respectively), Pfizer Inc. (PF-06939926), Sarepta (SRP-9001 and Galgt2 gene therapy program), and Solid Biosciences Inc. (SGT-001). Gene editing treatments that are in preclinical development are also being pursued by Vertex Pharmaceuticals, Inc. (Vertex) and Sarepta. We are also aware of several companies targeting non-dystrophin mechanisms for the treatment of DMD.

We expect to face competition from existing products and products in development for each of our therapeutic candidates. There are currently no approved therapies to treat the underlying cause of DM1. Therapeutic candidates currently in development to treat DM1 include: tideglusib, a GSK3-ß inhibitor in late-stage clinical development by AMO Pharma Ltd. for the congenital phenotype of DM1; AOC-1001, an antibody linked siRNA in clinical development by Avidity; DYNE-101, an antibody fragment conjugated to an ASO targeting DM1 protein kinase knockdown in preclinical development by Dyne; a peptide-nucleic acid targeting CUG repeats in development by NeuBase Therapeutics, Inc.; EDODM1, a linear peptide conjugated to a PMO targeting CUG repeats in preclinical development by PepGen, Inc.; a small molecule targeting GTG repeats in preclinical development by Design Therapeutics, Inc.; gene editing treatments in preclinical development by Vertex; an RNA-targeting gene therapy in preclinical development by Locana, Inc.; and small molecules interacting with RNA in preclinical development by Expansion Therapeutics, Inc.

The only currently-approved therapies for Pompe disease are alglucosidase alfa (Lumizyme in the United States, Myozyme in other geographies) and avalglucosidase alfa-ngpt (Nexviazyme in the United States), which are both forms of ERT delivered via IV infusions. There is one next-generation GAA enzyme in registration from Amicus Therapeutics Inc. (Amicus), and there are four gene therapies in the early stages of clinical development from Astellas Pharma Inc., Bayer AG, Roche Holding AG and Lacerta Therapeutics, Inc. There are five gene therapies in preclinical development from AVROBIO, Inc., Amicus, Provention Bio Inc., Selecta Biosciences, Inc. and Sarepta. There are two preclinical therapies targeting GYS1 inhibition from Maze Therapeutics, Inc. and Avidity, respectively. Denali has an ERT in preclinical development.

Many of our competitors have significantly greater financial, technical, manufacturing, marketing, sales and supply resources or experience than we do. If we successfully obtain approval for any therapeutic candidate, we will face competition based on many different factors, including the safety and effectiveness of our therapeutics, the ease with which our therapeutics 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, reimbursement coverage and patent position. Competing products could present superior treatment alternatives, including by being more effective, safer, more convenient, less expensive or marketed and sold more effectively than any products we may develop. Competitive products or technological approaches may make any products we develop, or our EEV Platform, obsolete or noncompetitive before we recover the expense of developing and commercializing our therapeutic candidates. If we are unable to compete effectively, our opportunity to generate revenue from the sale of our therapeutics we may develop, if approved, could be adversely affected.

Risks Related to Our Business Operations and Industry

Our future success depends on our ability to retain key employees and to attract, retain and motivate qualified personnel.

We are highly dependent on the research expertise of Natarajan Sethuraman, Ph.D., our Chief Scientific Officer, and the development and management expertise of Dipal Doshi, our President and Chief Executive Officer, as well as the other principal members of our management, scientific and clinical team. Although we have entered into employment agreements and/or offer letters with our executive officers, each of them may terminate their employment with us at any time.

Our industry has experienced a high rate of turnover in recent years. Our ability to compete in the highly competitive pharmaceuticals industry depends upon our ability to attract, retain and motivate highly skilled and experienced personnel with scientific, clinical, regulatory, manufacturing and management skills and experience. We conduct our operations in the Boston area, a region that is home to many other pharmaceutical companies as well as many academic and research institutions, resulting in fierce competition for qualified personnel. We may not be able to attract or retain qualified personnel in the future due to the intense competition for a limited number of qualified personnel among pharmaceutical companies. Many of the other pharmaceutical companies against which we compete have greater financial and other resources, different risk profiles and a longer history in the industry than we do. Our competitors may provide higher compensation, more diverse opportunities and/or better opportunities for career advancement. Any or all of these competing factors may limit our ability to continue to attract and retain high quality personnel, which could negatively affect our ability to successfully develop and commercialize our therapeutic candidates and to grow our business and operations as currently contemplated.

To induce valuable employees to remain at our company, in addition to salary and cash incentives, we have provided stock options that vest over time. The value to employees of stock options that vest over time may be significantly affected by movements in our stock price that are beyond our control and may at any time be insufficient to counteract more lucrative offers from other companies. Despite our efforts to retain valuable employees, members of our management, scientific and development teams may terminate their employment with us on short notice. For example, employment of our key employees is at-will, which means that any of our employees could leave our employment at any time, with or without notice.

In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us.

Our success also depends on our ability to continue to attract, retain and motivate highly skilled junior, mid-level and senior managers as well as junior, mid-level and senior scientific and medical personnel. Failure to succeed in clinical trials may make it more challenging to recruit and retain qualified scientific personnel.

We expect to expand our development and regulatory capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

As of February 28, 2022, we had 114 full-time employees. We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of clinical development, clinical operations, manufacturing, regulatory affairs and, if any of our therapeutic candidates receives marketing approval, sales, marketing and distribution. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth and with developing sales, marketing and distribution infrastructure, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources.

Further, we currently rely, and for the foreseeable future will continue to rely, in substantial part on certain third-party contract organizations, advisors and consultants to provide certain services, including assuming substantial responsibilities for the conduct of our clinical trials and the manufacture of ENTR-601-44 or any future therapeutic candidates. We cannot assure our stockholders that the services of such third-party contract organizations, advisors and consultants will continue to be available to us on a timely basis when needed, or that we can find qualified replacements. In addition, if we are unable to effectively manage our outsourced activities or if the quality or accuracy of the services provided by our vendors or consultants is compromised for any reason, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain marketing approval of ENTR-601-44 or any future therapeutic candidates or otherwise advance our business. We cannot assure our stockholders that we will be able to properly manage our existing vendors or consultants or find other competent outside vendors and consultants on economically reasonable terms, or at all.

If we are not able to effectively manage growth and expand our organization, we may not be able to successfully implement the tasks necessary to further develop and commercialize ENTR-601-44, our other development portfolio therapeutic candidates or any future therapeutic candidates and, accordingly, may not achieve our research, development and commercialization goals.

Recently enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our therapeutic candidates and decrease the prices we may obtain.

In the United States and some foreign 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 therapeutic candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any therapeutic candidates for which we obtain marketing approval.

For example, the ACA was passed in March 2010 and substantially changed the way healthcare is financed by both governmental and private insurers, and continues to significantly impact the U.S. pharmaceutical industry.

Among the provisions of the ACA of importance to our potential therapeutic candidates are the following:

- annual fees and taxes on manufacturers of certain branded prescription drugs;
- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic products;
- a new Medicare Part D coverage gap discount program, in which manufacturers must now agree to offer 70% (increased pursuant to the Bipartisan Budget Act of 2018, effective as of January 1, 2019) point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer’s outpatient drugs to be covered under Medicare Part D;

- 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;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations;
- expansion of healthcare fraud and abuse laws, including the False Claims Act and the federal Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance;
- extension of manufacturers' Medicaid rebate liability;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- requirements to report financial arrangements with physicians and teaching hospitals;
- a requirement to annually report drug samples that manufacturers and distributors provide to physicians; and
- a Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

Since its enactment, there have been numerous judicial, administrative, executive, and legislative challenges to certain aspects of the ACA. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court's decision, President Biden issued an Executive Order to initiate a special enrollment period from February 15, 2021 through August 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The Executive Order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is unclear how other healthcare reform measures of the Biden administrations or other efforts, if any, to challenge repeal or replace the ACA, will impact our business.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. On August 2, 2011, the Budget Control Act of 2011 was signed into law, which, among other things, created the Joint Select Committee on Deficit Reduction to recommend to Congress proposals for spending reductions. The Joint Select Committee did not achieve a targeted deficit reduction, triggering the legislation's automatic reduction to several government programs. These changes include aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, starting in 2013, and due to subsequent legislative amendments to the statute, will remain in effect through 2030, except for a temporary suspension from May 1, 2020 through March 31, 2022 due to the COVID-19 pandemic. Following the temporary suspension, a 1% payment reduction will occur beginning April 1, 2022 through June 30, 2022, and the 2% payment reduction will resume on July 1, 2022. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, reduced Medicare payments to several providers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. On April 13, 2017, CMS published a final rule that gives states greater flexibility 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. In addition, on December 20, 2019, former President Trump signed into law the Further Consolidated Appropriations Act (H.R. 1865), which repeals the Cadillac tax, the health insurance provider tax, and the medical device excise tax. It is impossible to determine whether similar taxes could be instated in the future. Further, CMS published a final rule that would give states greater flexibility as of 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. Additionally, in May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option of using step therapy for Part B drugs beginning January 1, 2020. However, it is unclear whether the Biden administration will challenge, reverse, revoke or otherwise modify these executive and administrative actions.

Further, there has been heightened governmental scrutiny recently over the manner in which drug 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. At the federal level, President Biden signed an Executive Order on July 9, 2021 affirming the administration's policy to (i) support legislative reforms that would lower the prices of prescription drug and biologics, including by allowing Medicare to negotiate drug prices, by imposing inflation caps, and, by supporting the development and market entry of lower-cost generic drugs and biosimilars; and (ii) support the enactment of a public health insurance option. Among other things, the Executive Order also directs HHS to provide a report on actions to combat excessive pricing of prescription drugs, enhance the domestic drug supply chain, reduce the price that the Federal government pays for drugs, and address price gouging in the industry; and directs the FDA to work with states and Indian Tribes that propose to develop section 804 Importation Programs in accordance with the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, and the FDA's implementing regulations. FDA released such implementing regulations on September 24, 2020, which went into effect on November 30, 2020, providing guidance for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020 CMS issued an Interim Final Rule implementing the Most Favored Nation (MFN) Model under which Medicare Part B reimbursement rates will be calculated for certain drugs and biologicals based on the lowest price drug manufacturers receive in Organization for Economic Cooperation and Development countries with a similar gross domestic product per capita. However, CMS published a final rule in the Federal Register on December 27, 2021 that rescinds the November 27, 2020 MFN Model interim final rule. Additionally, on December 2, 2020, HHS published a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. Pursuant to court order, the removal and addition of the aforementioned safe harbors were delayed and recent legislation imposed a moratorium on implementation of the rule until January 1, 2026. Although a number of these and other proposed measures may require authorization through additional legislation to become effective, and the Biden administration may reverse or otherwise change these measures, both the Biden administration and Congress have indicated that it will continue to seek new legislative measures to control drug costs.

At the state level, legislatures have 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.

We expect that the ACA, as well as other healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our therapeutics. Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. Legally mandated price controls on payment amounts by third-party payors or other restrictions could harm our business, financial condition, results of operations and prospects. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our therapeutic candidates, if any, may be. It is also possible that additional governmental action is taken in response to the ongoing COVID-19 pandemic.

Failure or security breaches, loss or leakage of data and other disruptions of our internal information technology systems, or those of our third-party CROs or other vendors, contractors or consultants could result in material disruption of our development programs, compromise sensitive information related to our business or prevent us from accessing critical information, potentially exposing us to liability or otherwise adversely affecting our business.

We are increasingly dependent upon information technology systems, infrastructure and data to operate our business. In the ordinary course of business, we collect, store and transmit confidential information (including but not limited to intellectual property, proprietary business information and personal information). It is critical that we do so in a secure manner to maintain the confidentiality and integrity of such confidential information. We also have outsourced

elements of our operations to third parties, and as a result we manage a number of third-party CROs, vendors, and other contractors and consultants who have access to our confidential information.

Despite the implementation of security measures, given their size and complexity and the increasing amounts of confidential information that they maintain, our internal information technology systems and those of our third-party CROs, vendors and other contractors and consultants are potentially vulnerable to breakdown or other damage or interruption from service interruptions, system malfunction, natural disasters, terrorism, war and telecommunication and electrical failures, as well as security breaches from inadvertent or intentional actions by our employees, third-party CROs, vendors, contractors, consultants, business partners and/or other third parties, or from cyber-attacks by malicious third parties (including the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information), which may compromise our system infrastructure, or that of our third-party CROs, vendors and other contractors and consultants, or lead to data leakage. The risk of a security breach or disruption, particularly through cyber-attacks or cyber intrusion, including by computer hackers, foreign governments, and cyber terrorists, has generally increased as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased. We may not be able to anticipate all types of security threats, nor may we be able to implement preventive measures effective against all such security threats. The techniques used by cyber criminals change frequently, may not be recognized until launched and can originate from a wide variety of sources, including outside groups such as external service providers, organized crime affiliates, terrorist organizations or hostile foreign governments or agencies. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or those of our third-party CROs, vendors and other contractors and consultants, or inappropriate disclosure of confidential or proprietary information, we could incur liability and reputational damage and the further development and commercialization of ENTR-601-44 or any future therapeutic candidates could be delayed. The costs related to significant security breaches or disruptions could be material and exceed the limits of the cybersecurity insurance we maintain against such risks. If the information technology systems of our third-party CROs, vendors and other contractors and consultants become subject to disruptions or security breaches, we may have insufficient recourse against such third parties and we may have to expend significant resources to mitigate the impact of such an event, and to develop and implement protections to prevent future events of this nature from occurring.

Our data protection efforts and our investment in information technology will prevent significant breakdowns, data leakages, breaches in our systems, or those of our third-party CROs, vendors and other contractors and consultants, or other cyber incidents that could have a material adverse effect upon our reputation, business, operations or financial condition. For example, if such an event were to occur and cause interruptions in our operations, or those of our third-party CROs, vendors and other contractors and consultants, it could result in a material disruption of our programs and the development of our therapeutic candidates could be delayed. In addition, the loss of clinical trial data for ENTR-601-44 or any other therapeutic candidates could result in delays in our marketing approval efforts and significantly increase our costs to recover or reproduce the data. Furthermore, significant disruptions of our internal information technology systems or those of our third-party CROs, vendors and other contractors and consultants, or security breaches could result in the loss, misappropriation and/or unauthorized access, use, or disclosure of, or the prevention of access to, confidential information (including trade secrets or other intellectual property, proprietary business information and personal information), which could result in financial, legal, business and reputational harm to us. For example, any such event that leads to unauthorized access, use, or disclosure of personal information, including personal information regarding our clinical trial subjects or employees, could harm our reputation directly, compel us to comply with federal and/or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, and otherwise subject us to liability under laws and regulations that protect the privacy and security of personal information, which could result in significant legal and financial exposure and reputational damages that could potentially have an adverse effect on our business.

A pandemic, epidemic or outbreak of an infectious disease, such as COVID-19, may materially and adversely affect our business and could cause a disruption to the development of our therapeutic candidates.

The ongoing COVID-19 pandemic continues to rapidly evolve and has broadly affected the global economy, resulted in significant travel and work restrictions in many regions and has put a significant strain on healthcare resources. The ultimate extent of the impact of the COVID-19 pandemic on our business, preclinical studies and planned clinical trials, financial condition and results of operations is highly uncertain and will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the identification of new variants of the virus, the duration of the pandemic, travel restrictions and social distancing 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. The continuation of the worldwide COVID-19 pandemic may affect our ability to initiate and complete preclinical studies,

delay the initiation of our planned clinical trials, disrupt regulatory activities or have other adverse effects on our business, results of operations, financial condition and prospects. In addition, the ongoing COVID-19 pandemic has adversely impacted economies worldwide and may cause substantial disruption in the financial markets, both of which could adversely affect our business, operations and ability to raise funds to support our operations.

To date, we have not experienced a material financial impact or significant business disruptions, including with our vendors, or impairments of any of our assets as a result of the ongoing COVID-19 pandemic. We are following, and plan to continue to follow, recommendations from federal, state and local governments regarding workplace policies, practices and procedures. We have taken temporary precautionary measures intended to help minimize the risk of the virus to our employees, including limiting on-site presence to essential employees, providing for social distancing, increased sanitization of our facilities and providing personal protective equipment for our employees. We expect to continue to take actions as may be required or recommended by government authorities or as we determine are in the best interests of our employees and other business partners. We are continuing to monitor the potential impact of the ongoing COVID-19 pandemic, but we cannot be certain what the overall impact of the COVID-19 pandemic will be on our business, financial condition, results of operations and prospects.

Failure to comply with environmental, health and safety laws and regulations could subject us to fines or penalties or incur costs that could harm our business.

We are subject to numerous foreign, federal, state and local environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources, including any available insurance.

In addition, our leasing and operation of real property may subject us to liability pursuant to certain of these laws or regulations. Under existing U.S. environmental laws and regulations, current or previous owners or operators of real property and entities that disposed or arranged for the disposal of hazardous substances may be held strictly, jointly and severally liable for the cost of investigating or remediating contamination caused by hazardous substance releases, even if they did not know of and were not responsible for the releases.

We could incur significant costs and liabilities which may adversely affect our financial condition and operating results for failure to comply with such laws and regulations, including, among other things, civil or criminal fines and penalties, property damage and personal injury claims, costs associated with upgrades to our facilities or changes to our operating procedures, or injunctions limiting or altering our operations.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not 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.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations, which are becoming increasingly more stringent, may impair our research, development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Our relationships with customers, third-party payors, physicians and healthcare providers will be subject to applicable anti-kickback, fraud and abuse, and other laws and regulations, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm, and diminished profits.

Healthcare providers, physicians and third-party payors will play a primary role in the recommendation and prescription of any therapeutic candidates for which we obtain regulatory approval. Our current and future arrangements with third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we conduct research and would market, sell and distribute our therapeutics. As a pharmaceutical company, even though we do not and will not

control referrals of healthcare services or bill directly to Medicare, Medicaid or other third-party payors, federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to our business. Restrictions under applicable federal and state healthcare laws and regulations that may affect our ability to operate include the following:

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

- the federal civil and criminal false claims laws and civil monetary penalty laws, such as the federal False Claims Act, which impose criminal and civil penalties and authorize civil whistleblower or qui tam actions, against individuals or entities for, among other things: knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent; knowingly making, using or causing to be made or used, a false statement of record material to a false or fraudulent claim or obligation to pay or transmit money or property to the federal government or knowingly concealing or knowingly and improperly avoiding or decreasing an obligation to pay money to the federal government. Manufacturers can be held liable under the federal False Claims Act even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims. The federal False Claims Act also permits a private individual acting as a "whistleblower" to bring actions on behalf of the federal government alleging violations of the federal False Claims Act and to share in any monetary recovery;

- the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA), which created new federal criminal statutes that prohibit a person from knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious, or fraudulent statements or representations in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 (HITECH) and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates, independent contractors or agents of covered entities, that perform services for them that involve the creation, maintenance, receipt, use, or disclosure of, individually identifiable health information relating to the privacy, security and transmission of individually identifiable health information. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, there may be additional federal, state and non-U.S. laws which govern the privacy and security of health and other personal information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts;

- the U.S. federal transparency requirements under the ACA, including the provision commonly referred to as the Physician Payments Sunshine Act, and its implementing regulations, which requires applicable manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program to report annually to CMS, information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members. Effective January 1, 2022, obligations extend to include transfers of value made to certain non-physician providers (physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists and anesthesiologist assistants and certified-nurse midwives);

- federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs; and

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

Additionally, we are subject to state and foreign equivalents of each of the healthcare laws and regulations described above, among others, some of which may be broader in scope and may apply regardless of the payor. Many U.S. states have adopted laws similar to the federal Anti-Kickback Statute and False Claims Act, and may apply to our business practices, including, but not limited to, research, distribution, sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental payors, including private insurers. In addition, some states have passed laws that require pharmaceutical companies to comply with the April 2003 Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers and/or the Pharmaceutical Research and Manufacturers of America's Code on Interactions with Healthcare Professionals. Several states also impose other marketing restrictions or require pharmaceutical companies to make marketing or price disclosures to the state and require the registration of pharmaceutical sales representatives. State and foreign laws, including for example the European Union General Data Protection Regulation, which became effective on May 25, 2018 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. There are ambiguities as to what is required to comply with these state requirements and if we fail to comply with an applicable state law requirement we could be subject to penalties. Finally, there are state and foreign laws governing the privacy and security of health information, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

The scope and enforcement of each of these laws is uncertain and subject to rapid change in the current environment of healthcare reform, especially in light of the lack of applicable precedent and regulations. Federal and state enforcement bodies have recently increased their scrutiny of interactions between healthcare companies and healthcare providers, which has led to a number of investigations, prosecutions, convictions and settlements in the healthcare industry. Ensuring business arrangements comply with applicable healthcare laws, as well as responding to possible investigations by government authorities, can be time and resource consuming and can divert a company's attention from the business.

Ensuring that our internal operations and future business arrangements with third parties comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations, agency guidance or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of the laws described above or any other governmental laws and regulations that may apply to us, we may be subject to significant penalties, including administrative, civil and criminal penalties, damages, fines, disgorgement, the exclusion from participation in federal and state healthcare programs, individual imprisonment, reputational harm, and the curtailment or restructuring of our operations, as well as additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws. Further, defending against any such actions can be costly and time-consuming, and may require significant financial and personnel resources. Therefore, even if we are successful in defending against any such actions that may be brought against us, our business may be impaired. If any of the physicians or other providers or entities with whom we expect to do business is found to not be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs and imprisonment. If any of the above occur, our ability to operate our business and our results of operations could be adversely affected.

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

We are exposed to the risk that our employees and independent contractors, including principal investigators, CROs, consultants and vendors may engage in misconduct or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or disclosure of unauthorized activities to us that violate: (i) the laws and regulations of the FDA and other similar regulatory requirements, including those laws that require the reporting of true, complete and accurate information to such authorities, (ii) manufacturing standards, including cGMP requirements, (iii) federal and state data privacy, security, fraud and abuse and other healthcare laws and regulations in the United States and abroad or (iv) laws that require the true, complete and accurate reporting of financial information or data. Activities subject to these laws also involve the improper use or misrepresentation of information obtained in the course of clinical trials, the creation of fraudulent data in our preclinical studies or clinical trials or illegal misappropriation of drug product, which could result in regulatory sanctions and cause serious harm to our reputation. It is not always possible to identify and deter misconduct by employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. In addition, we are subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. 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 and financial results, including, without limitation, the imposition of significant civil, criminal and administrative penalties, damages, monetary fines, disgorgements, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, imprisonment, contractual damages, reputational harm, diminished profits and future earnings, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

We are subject to certain U.S. and certain foreign anti-corruption, anti-money laundering, export control, sanctions and other trade laws and regulations. We can face serious consequences for violations.

U.S. and foreign anti-corruption, anti-money laundering, export control, sanctions and other trade laws and regulations prohibit, among other things, companies and their employees, agents, CROs, legal counsel, accountants, consultants, contractors and other partners from authorizing, promising, offering, providing, soliciting, or receiving directly or indirectly, corrupt or improper payments or anything else of value to or from recipients in the public or private sector. Violations of these laws can result in substantial criminal fines and civil penalties, imprisonment, the loss of trade privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm and other consequences. We have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities and other organizations. We also expect our non-U.S. activities to increase over time. We expect to rely on third parties for research, preclinical studies and clinical trials and/or to obtain necessary permits, licenses, patent registrations and other marketing approvals. We can be held liable for the corrupt or other illegal activities of our personnel, agents, or partners, even if we do not explicitly authorize or have prior knowledge of such activities.

Any violations of the laws and regulations described above may result in substantial civil and criminal fines and penalties, imprisonment, the loss of export or import privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm and other consequences.

We may engage in strategic transactions that could impact our liquidity, increase our expenses and present significant distractions to our management.

From time to time, we may consider strategic transactions, such as acquisitions of companies, asset purchases and out-licensing or in-licensing of intellectual property, products or technologies. Additional potential transactions that we may consider in the future include a variety of business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and investments. Any future transactions could increase our near and long-term expenditures, result in potentially dilutive issuances of our equity securities, including our common stock, or the incurrence of debt, contingent liabilities, amortization expenses or acquired in-process research and development expenses, any of which could affect our financial condition, liquidity and results of operations. Future acquisitions may also require us to obtain additional financing, which may not be available on favorable terms or at all. These transactions may never be

successful and may require significant time and attention of our management. In addition, the integration of any business that we may acquire in the future may disrupt our existing business and may be a complex, risky and costly endeavor for which we may never realize the full benefits of the acquisition. Moreover, we may not be able to locate suitable acquisition opportunities and this inability could impair our ability to grow or obtain access to technology or products that may be important to the development of our business. Accordingly, although there can be no assurance that we will undertake or successfully complete any additional transactions of the nature described above, any additional transactions that we do complete could have a material adverse effect on our business, results of operations, financial condition and prospects.

Legislation or other changes in U.S. tax law could adversely affect our business and financial condition.

The rules dealing with U.S. federal, state, and local income taxation are constantly under review by persons involved in the legislative process and by the Internal Revenue Service and the U.S. Treasury Department. Changes to tax laws (which changes may have retroactive application) could adversely affect us or holders of our common stock. In recent years, many changes have been made to applicable tax laws and changes are likely to continue to occur in the future. For example, the Tax Cuts and Jobs Act (the TCJA) was enacted in 2017 and made significant changes to corporate taxation, including the reduction of the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, the limitation of the tax deduction for net interest expense to 30% of adjusted taxable income (except for certain small businesses), the limitation of the deduction for net operating losses to 80% of current year taxable income and the elimination of net operating loss carrybacks (though any such net operating losses may be carried forward indefinitely) and the modification or repeal of many business deductions and credits, in each case, as modified by the CARES Act (as defined below). In addition, on March 27, 2020, former President Trump signed into law the Coronavirus Aid, Relief, and Economic Security Act (the CARES Act), which included certain changes in tax law intended to stimulate the U.S. economy in light of the ongoing COVID-19 coronavirus pandemic, including temporary beneficial changes to the treatment of net operating losses, interest deductibility limitations and payroll tax matters. Under the CARES Act, the limitation of the tax deduction for net operating losses to 80% of taxable income applies only to taxable years beginning after December 31, 2020 and net operating losses generated in 2018, 2019 and 2020 may be carried back five taxable years. Further, under the CARES Act, the limitation of the tax deduction for net interest expense to 30% of adjusted taxable income is increased to 50% of adjusted taxable income for 2019 and 2020. Future changes in tax laws could have a material adverse effect on our business, cash flow, financial condition or results of operations.

It cannot be predicted whether, when, in what form, or with what effective dates, new tax laws may be enacted, or regulations and rulings may be enacted, promulgated or issued under existing or new tax laws, which could result in an increase in our or our stockholders' tax liability or require changes in the manner in which we operate in order to minimize or mitigate any adverse effects of changes in tax law or in the interpretation thereof. We urge investors to consult with their legal and tax advisers regarding the implications of potential changes in tax laws on an investment in our common stock.

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

Our ability to use our U.S. federal and state net operating losses to offset potential future taxable income and related income taxes that would otherwise be due is dependent upon our generation of future taxable income, and we cannot predict with certainty when, or whether, we will generate sufficient taxable income to use all of our net operating losses.

Under current law, unused U.S. federal net operating losses generated for tax years beginning after December 31, 2017 are not subject to expiration and may be carried forward indefinitely. Such U.S. federal net operating losses generally may not be carried back to prior taxable years, except that, net operating losses generated in 2018, 2019 and 2020 may be carried back to each of the five tax years preceding the tax years of such losses. Additionally, for taxable years beginning after December 31, 2020, the deductibility of such U.S. federal net operating losses is limited to 80% of our taxable income in any future taxable year. In addition, both our current and our future unused U.S. federal net operating losses and tax credits may be subject to limitation under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended (Code), if we undergo an "ownership change," generally defined as a greater than 50 percentage point change (by value) in its equity ownership by certain stockholders over a rolling three-year period. We may have experienced such ownership changes in the past, and we may experience ownership changes in the future as a result of shifts in our stock ownership, some of which are outside our control. Our net operating losses and tax credits may also be impaired or restricted under state law. As of December 31, 2021, we had U.S. federal net operating loss carryforwards of approximately $93.1 million, and our ability to utilize those net operating loss carryforwards could be limited by an "ownership change" as described above, which could result in increased tax liability to us.

We plan to distribute our technology, biology, execution and financing risks across a wide variety of therapeutic areas, disease states, programs, and technologies. However, our assessment of, and approach to, risk may not be comprehensive or effectively avoid delays or failures in one or more of our programs or modalities. Failures in one or more of our programs or modalities could adversely impact other programs or modalities in our development portfolio and have a material adverse impact on our business, results of operations and ability to fund our business.

We are creating a new category of potential therapeutics based on EEVs to improve the lives of patients. We have designed our strategy and operations to realize the full potential value and impact of EEVs over a long time horizon across a broad array of human diseases. We have made investments in our platform, infrastructure, and clinical capabilities that have enabled us to establish a development portfolio of several programs in development. As our therapeutic candidates and discovery programs progress, we or others may determine: that certain of our risk allocation decisions were incorrect or insufficient; that we made platform level technology mistakes; that individual programs or our EEV science in general has technology or biology risks that were unknown or underappreciated; that our choices on how to develop our infrastructure to support our scale will result in an inability to manufacture our therapeutics for clinical trials or otherwise impair our manufacturing; or that we have allocated resources in such a way that large investments are not recovered and capital allocation is not subject to rapid re-direction. All of these risks may relate to our current and future programs sharing similar science (including EEV science) and infrastructure, and in the event material decisions in any of these areas turn out to have been incorrect or under-optimized, we may experience a material adverse impact on our business and ability to fund our operations and we may never realize what we believe is the potential of EEVs.

While we will attempt to diversify our risks by developing one or more programs in each modality, there are risks that are unique to each modality and risks that are applicable across modalities. These risks may impair our ability to advance one or more of our programs in clinical development, obtain regulatory approval, or ultimately commercialize our programs, or cause us to experience significant delays in doing so, any of which may materially harm our business.

Certain features in our therapeutic candidates, including those related to large enzymes, antibodies and oligonucleotides, and their components, may result in foreseen and unforeseen risks that are active across some or all of our modalities. In addition, the biology risk across much of our development portfolio represents targets and pathways not clinically validated by one or more approved drugs. While we believe we have made progress in seeking to reduce biology risk in certain settings, the risk that the targets or pathways that we have selected may not be effective could continue to apply across our current and future programs. Any such portfolio spanning risks, whether known or unknown, if realized in any one of our programs would have a material and adverse effect on our other programs and on our business as a whole.

Successful development of intracellular therapeutics is highly uncertain and is dependent on numerous factors, many of which are beyond our control. Intracellular therapeutics that appear promising in the early phases of development may fail to reach the market for several reasons, including:

- nonclinical or preclinical testing or study results may show our EEV-therapeutics to be less effective than desired or to have harmful or problematic side effects or toxicities;
- clinical trial results may show our oligonucleotides to be less effective than expected (e.g., a clinical trial could fail to meet its primary endpoint(s)) or to have unacceptable side effects or toxicities;
- failure to receive the necessary regulatory approvals or a delay in receiving such approvals. Among other things, such delays may be caused by slow enrollment in clinical trials, patients dropping out of trials, length of time to achieve trial endpoints, additional time requirements for data analysis, NDA or BLA preparation, discussions with the FDA, an FDA request for additional nonclinical or clinical data, or unexpected safety or manufacturing issues;
- manufacturing costs, formulation issues, pricing or reimbursement issues, or other factors that make our EEV-therapeutics uneconomical; and
- proprietary rights of others and their competing products and technologies that may prevent our EEV-therapeutics from being commercialized.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain patent protection for our therapeutic programs and other proprietary technologies we develop, or if the scope of the patent protection obtained is not sufficiently broad, our competitors could develop and commercialize products and technology similar or identical to ours, and our ability to successfully commercialize our therapeutic programs and other proprietary technologies we may develop may be adversely affected.

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our therapeutic programs and other proprietary technologies we may develop. In order to protect our proprietary position, we have filed or intend to file patent applications in the United States and abroad relating to our therapeutic programs and other proprietary technologies we may develop; however, there can be no assurance that any such patent applications will issue as granted patents. If we are unable to obtain or maintain patent protection with respect to our therapeutic programs and other proprietary technologies we may develop, our business, financial condition, results of operations and prospects could be materially harmed.

Changes in either the patent laws or their interpretation in the United States and other countries may diminish our ability to protect our inventions, obtain, maintain and enforce our intellectual property rights and, more generally, could affect the value of our intellectual property or narrow the scope of our protection. In addition, we may rely on third-party collaborators or licensors to file patent applications relating to therapeutic programs or proprietary technology that may be developed or in-licensed. We cannot predict whether the patent applications we are currently pursuing, or that we or our third-party collaborators or licensors may pursue, will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient protection against competitors or other third parties.

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

No consistent policy regarding the scope of claims allowable in patents in the biotechnology field has emerged in the United States, and the patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has been the subject of much litigation in recent years. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our patent applications may not result in patents being issued which protect our therapeutic programs and other proprietary technologies we may develop or which effectively prevent others from commercializing competitive technologies and products. In particular, our ability to stop third parties from making, using, selling, offering to sell, or importing products that infringe our intellectual property will depend in part on our success in obtaining and enforcing patent claims that cover our technology, inventions and improvements. We do not currently have issued patents that cover all of our technology or therapeutic candidates. With respect to both licensed and company-owned intellectual property, we cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future. Moreover, even issued patents do not provide us with the right to practice our technology in relation to the commercialization of our therapeutics. The area of patent and other intellectual property rights in biotechnology is an evolving one with many risks and uncertainties, and third parties may have blocking patents that could be used to prevent us from commercializing our patented therapeutic candidates and practicing our proprietary technology. Our issued patents, those that may issue in the future and those that we in-license may be challenged, invalidated, or circumvented, which could limit our ability to stop competitors from marketing related products or limit the length of the term of patent protection that we may have for our therapeutic candidates. Furthermore, our competitors may independently develop similar technologies.

Moreover, the claim coverage in a patent application can be significantly reduced before the patent is granted. Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us or otherwise provide us with any competitive advantage. Any patents issuing from our patent applications may be challenged, narrowed, circumvented or invalidated by third parties. Consequently, we do not know whether our therapeutic programs and other proprietary technology will be protectable or remain protected by valid and enforceable patents. For example, we do not currently have any issued patents covering any of our oligonucleotide therapeutic candidates. The extent to which any patents, if and when granted, will cover our therapeutic candidates is uncertain. Even if a patent is granted, our competitors or other third parties may be able to circumvent the patent by developing similar or alternative technologies or products in a non-infringing manner which could materially adversely affect our business, financial condition, results of operations and prospects. In addition, given the amount of time required for the development, testing and regulatory review of our therapeutic programs and eventual therapeutic candidates, patents protecting the therapeutic candidates might expire before or shortly after such therapeutic candidates are commercialized. As a result, our intellectual property may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

The issuance of a patent is not conclusive as to its inventorship, scope, validity, or enforceability and our patents may be challenged in the courts or patent offices in the United States and abroad. We may be subject to a third-party pre-issuance submission of prior art to the United States Patent and Trademark Office (USPTO) or in other jurisdictions, or become involved in opposition, derivation, revocation, reexamination, post-grant and *inter partes* review, or other similar proceedings challenging our patent rights. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate or render unenforceable, our patent rights, allow third parties to commercialize our therapeutic programs and other proprietary technologies we may develop and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. Such proceedings also may result in substantial cost and require significant time from our scientists and management, even if the eventual outcome is favorable to us.

In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, regardless of the outcome, it could dissuade companies from collaborating with us to license, develop or commercialize current or future therapeutic candidates.

Our rights to develop and commercialize any therapeutic candidates are subject and may in the future be subject, in part, to the terms and conditions of licenses granted to us by third parties. If we fail to comply with our obligations under our current or future intellectual property license agreements or otherwise experience disruptions to our business relationships with our current or any future licensors, we could lose intellectual property rights that are important to our business.

We are and expect to continue to be reliant upon third-party licensors for certain patent and other intellectual property rights that are important or necessary to the development of our therapeutic programs, eventual therapeutic candidates, and proprietary technologies. For example, we rely on a license from Ohio State Innovation Foundation (OSIF), an affiliate of The Ohio State University (OSU) to certain patent rights and know-how of OSU. Our license agreement with OSIF imposes, and we expect that any future license agreement will impose, specified diligence, milestone payments, royalty payments, commercialization, development and other obligations on us and require us to meet development timelines, or to exercise diligent or commercially reasonable efforts to develop and commercialize licensed products, in order to maintain the licenses. These milestone payments, and other payments associated with the license, will make it less profitable for us to develop and potentially commercialize our therapeutic candidate. If this agreement is terminated, we could lose intellectual property rights that may be important to our business, potentially be liable for damages to the licensor or potentially be prevented from developing and commercializing our therapeutic candidate. Termination of the agreement or reduction or elimination of our rights under the agreement may also potentially result in us being required to negotiate a new or reinstated agreement with less favorable terms, and it is possible that we may be unable to obtain any such additional license at a reasonable cost or on reasonable terms, if at all. In that event, we may be required to spend significant time and resources to redesign our therapeutic candidate or the method for manufacturing it or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. For more information on the terms of the license agreement with OSIF, see “Business-Intellectual Property-License Agreement with The Ohio State University” in our final prospectus filed with the SEC pursuant to Rule 424(b)(4) under the Securities Act on November 1, 2021.

Furthermore, our licensors have, or may in the future have, the right to terminate a license if we materially breach the agreement and fail to cure such breach within a specified period or in the event we undergo certain bankruptcy events. In spite of our best efforts, our current or any future licensors might conclude that we have materially breached our license agreements and might therefore terminate the license agreements. If our license agreements are terminated, we may lose our rights to develop and commercialize therapeutic candidates and technology, lose patent protection, experience significant delays in the development and commercialization of our therapeutic candidates and technology, and incur liability for damages. If these in-licenses are terminated, or if the underlying intellectual property fails to provide the intended exclusivity, our competitors or other third parties could have the freedom to seek regulatory approval of, and to market, products and technologies identical or competitive to ours and we may be required to cease our development and commercialization of certain of our therapeutic candidates and technology. In addition, we may seek to obtain additional licenses from our licensors and, in connection with obtaining such licenses, we may agree to amend our existing licenses in a manner that may be more favorable to the licensors, including by agreeing to terms that could enable third parties, including our competitors, to receive licenses to a portion of the intellectual property that is subject to our existing licenses and to compete with any therapeutic candidates we may develop and our technology. Any of the foregoing could have a material adverse effect on our competitive position, business, financial condition, results of operations and prospects.

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

- the scope of rights granted and obligations imposed under the license agreement and other interpretation-related issues;
- our or our licensors' ability to obtain, maintain and defend intellectual property and to enforce intellectual property rights against third parties;
- the extent to which our technology, therapeutic candidates and processes infringe, misappropriate or otherwise violate the intellectual property of the licensor that is not subject to the license agreement;
- the sublicensing of patent and other intellectual property rights under our license agreements;
- our diligence, development, regulatory, commercialization, financial or other obligations under the license agreement and what activities satisfy those diligence obligations;
- the inventorship and ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our current or future licensors and us and our partners; and
- the priority of invention of patented technology.

In addition, any current or future license agreements to which we are a party, including our license agreement with OSIF, are likely to be, complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology, or increase what we believe to be our diligence, development, regulatory, commercialization, financial or other obligations under the relevant agreement. In addition, if disputes over intellectual property that we have licensed or any other dispute related to our license agreements prevent or impair our ability to maintain our current license agreements on commercially acceptable terms, we may be unable to successfully develop and commercialize the affected therapeutic candidates and technology. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

License agreements we may enter into in the future may be non-exclusive. Accordingly, third parties may also obtain non-exclusive licenses from such licensors with respect to the intellectual property licensed to us under such license agreements. Accordingly, these license agreements may not provide us with exclusive rights to use such licensed patent and other intellectual property rights, or may not provide us with exclusive rights to use such patent and other intellectual property rights in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology and any therapeutic candidates we may develop in the future.

Moreover, some of our in-licensed patent and other intellectual property rights may in the future be subject to third party interests such as co-ownership. If we are unable to obtain an exclusive license to such third-party co-owners' interest,

in such patent and other intellectual property rights, such third-party co-owners may be able to license their rights to other third parties, including our competitors, and our competitors could market competing products and technology. We or our licensors may need the cooperation of any such co-owners of our licensed patent and other intellectual property rights in order to enforce them against third parties, and such cooperation may not be provided to us or our licensors.

Additionally, we may not have complete control over the preparation, filing, prosecution, maintenance, enforcement and defense of patents and patent applications that we license from third parties. It is possible that our licensors' filing, prosecution and maintenance of the licensed patents and patent applications, enforcement of patents against infringers or defense of such patents against challenges of validity or claims of enforceability may be less vigorous than if we had conducted them ourselves, and accordingly, we cannot be certain that these patents and patent applications will be prepared, filed, prosecuted, maintained, enforced and defended in a manner consistent with the best interests of our business. If our licensors fail to file, prosecute, maintain, enforce and defend such patents and patent applications, or lose rights to those patents or patent applications, the rights we have licensed may be reduced or eliminated, our right to develop and commercialize any of our technology and any therapeutic candidates we may develop that are the subject of such licensed rights could be adversely affected and we may not be able to prevent competitors or other third parties from making, using and selling competing products.

Furthermore, our owned and in-licensed patent rights may be subject to a reservation of rights by one or more third parties, including the U.S. government. Pursuant to the Bayh-Dole Act of 1980, the U.S. government has certain rights in inventions developed with government funding. These U.S. government rights include a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. When new technologies are developed with government funding, in order to secure ownership of patent rights related to the technologies, the recipient of such funding is required to comply with certain government regulations, including timely disclosing the inventions claimed in such patent rights to the U.S. government and timely electing title to such inventions. A failure to meet these obligations may lead to a loss of rights or the unenforceability of relevant patents or patent applications. In addition, the U.S. government has the right, under certain limited circumstances, to require us to grant exclusive, partially exclusive, or non-exclusive licenses to any of these inventions to a third party if it determines that: (1) adequate steps have not been taken to commercialize the invention; (2) government action is necessary to meet public health or safety needs; or (3) government action is necessary to meet requirements for public use under federal regulations (also referred to as "march-in rights"). If the U.S. government exercised its march-in rights in our current or future intellectual property rights that are generated through the use of U.S. government funding or grants, we could be forced to license or sublicense intellectual property developed by us or that we license on terms unfavorable to us, and there can be no assurance that we would receive compensation from the U.S. government for the exercise of such rights. If the U.S. government decides to exercise these rights, it is not required to engage us as its contractor in connection with doing so. The U.S. government's rights may also permit it to disclose the funded inventions and technology, which may include our confidential information, to third parties and to exercise march-in rights to use or allow third parties to use the technology that was developed using U.S. government funding. Intellectual property generated under a government funded program is also subject to certain reporting requirements, compliance with which may require us to expend substantial resources. In addition, the U.S. government requires that any products embodying any of these inventions or produced through the use of any of these inventions be manufactured substantially in the United States. This preference for U.S. industry may be waived by the federal agency that provided the funding if the owner or assignee of the intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible. This preference for U.S. industry may limit our ability to contract with non-U.S. product manufacturers for products covered by such intellectual property. Any of the foregoing could harm our business, financial condition, results of operations and prospects significantly.

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

Filing, prosecuting, maintaining, enforcing and defending patents and other intellectual property rights on our technology and any therapeutic candidates we may develop in all jurisdictions throughout the world would be prohibitively expensive, and accordingly, our intellectual property rights in some jurisdictions outside the United States could be less extensive than those in the United States. In some cases, we or our licensors may not be able to obtain patent or other intellectual property protection for certain technology and therapeutic candidates outside the United States. In addition, the laws of some foreign jurisdictions do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we and our licensors may not be able to obtain issued patents or other intellectual property rights covering any therapeutic candidates we may develop and our technology in all jurisdictions outside the United States and, as a result, may not be able to prevent third parties from practicing our and our licensors' inventions in all countries

outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Third parties may use our technologies in jurisdictions where we and our licensors have not pursued and obtained patent or other intellectual property protection to develop their own products and, further, may export otherwise infringing, misappropriating or violating products to territories where we have patent or other intellectual property protection, but enforcement is not as strong as that in the United States. These products may compete with any therapeutic candidates we may develop and our technology and our or our licensors' patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Additionally, many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain jurisdictions, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology and pharmaceutical products, which could make it difficult for us to stop the infringement, misappropriation or other violation of our patent and other intellectual property rights or marketing of competing products in violation of our intellectual property rights generally. For example, an April 2019 report from the Office of the United States Trade Representative identified a number of countries, including China, Russia, Argentina, Chile and India, where challenges to the procurement and enforcement of patent rights have been reported. Proceedings to enforce our or our licensors' patent and other intellectual property rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patent and other intellectual property rights at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We or our licensors may not prevail in any lawsuits that we or our licensors initiate and, if we or our licensors prevail, the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Many jurisdictions have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In addition, many jurisdictions limit the enforceability of patents against government agencies or government contractors. In these jurisdictions, the patent owner may have limited remedies, which could materially diminish the value of such patents. If we or any of our licensors is forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired, and our business, financial condition, results of operations and prospects may be adversely affected. Patent protection must ultimately be sought on a country-by-country basis, which is an expensive and time-consuming process with uncertain outcomes. Accordingly, we may choose not to seek patent protection in certain countries, and we will not have the benefit of patent protection in such countries.

Issued patents covering any therapeutic candidates we may develop could be found invalid or unenforceable if challenged in court or before administrative bodies in the United States or abroad.

Our owned and licensed patent rights may be subject to priority, validity, inventorship and enforceability disputes. If we or our licensors are unsuccessful in any of these proceedings, such patent rights may be narrowed, invalidated or held unenforceable, we may be required to obtain licenses from third parties, which may not be available on commercially reasonable terms or at all, or we may be required to cease the development, manufacture and commercialization of one or more of our therapeutic candidates. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

If we or one of our licensors initiate legal proceedings against a third party to enforce a patent covering any of any therapeutic candidates we may develop or our technology, the defendant could counterclaim that the patent covering the therapeutic candidate or technology is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, lack of written description or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld information material to patentability from the USPTO, or made a misleading statement, during prosecution. Third parties also may raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, interference proceedings, derivation proceedings, post grant review, *inter partes* review and equivalent proceedings such as opposition, invalidation and revocation proceedings in foreign jurisdictions. Such proceedings could result in the revocation or cancellation of or amendment to our patents in such a way that they no longer cover any therapeutic candidates we may develop or our technology or no longer prevent third parties from competing with any therapeutic candidates we may develop or our technology. The outcome following legal assertions of invalidity and unenforceability is unpredictable. Defense of these

claims, regardless of their merit, would involve substantial litigation expense and would be a distraction to management and other employees. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which the patent examiner and we or our licensing partners were unaware during prosecution. If a third party were to prevail on a legal assertion of invalidity or unenforceability, we could lose at least part, and perhaps all, of the patent protection on one or more of our therapeutic candidates or technology. Such a loss of patent protection could have a material adverse effect on our business, financial condition, results of operations and prospects.

Obtaining and maintaining our patent protection depends on compliance with various procedural, document submission, fee payment, and other requirements imposed by government patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees, renewal fees, annuity fees, and various other government fees on patents and applications will be due to be paid to the USPTO and various government patent agencies outside of the United States over the lifetime of our owned or licensed patents and applications. In certain circumstances, we rely on our licensing partners to pay these fees due to U.S. and non-U.S. patent agencies. The USPTO and various non-U.S. government agencies require compliance with several procedural, documentary, fee payment and other similar provisions during the patent application process. We are also dependent on our licensors to take the necessary action to comply with these requirements with respect to our licensed intellectual property. In some cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. There are situations, however, in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in a partial or complete loss of patent rights in the relevant jurisdiction. In such an event, potential competitors might be able to enter the market with similar or identical products or technology, which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

Changes in patent law in the United States or worldwide could diminish the value of patents in general, thereby impairing our ability to protect any therapeutic candidates we may develop and our technology.

Changes in either the patent laws or interpretation of patent laws in the United States and worldwide, including patent reform legislation such as the Leahy-Smith America Invents Act (the Leahy-Smith Act), could increase the uncertainties and costs surrounding the prosecution of any owned or in-licensed patent applications and the maintenance, enforcement or defense of any current in-licensed issued patents and issued patents we may own or in-license in the future. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These changes include provisions that affect the way patent applications are prosecuted, redefine prior art, provide more efficient and cost-effective avenues for competitors to challenge the validity of patents, and enable third-party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent at USPTO-administered post-grant proceedings, including post-grant review, *inter partes* review, and derivation proceedings. Assuming that other requirements for patentability are met, prior to March 2013, in the United States, the first to invent the claimed invention was entitled to the patent, while outside the United States, the first to file a patent application was entitled to the patent. After March 2013, under the Leahy-Smith Act, the United States transitioned to a first-to-file system in which, assuming that the other statutory requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third party was the first to invent the claimed invention. As such, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our in-licensed issued patents and issued patents we may own or in-license in the future, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects. Since patent applications in the United States and most other countries are confidential for a period of time after filing or until issuance, we cannot be certain that we or our licensors were the first to either (i) file any patent application related to our therapeutic candidates or (ii) invent any of the inventions claimed in our or our licensor's patents or patent applications.

The Leahy-Smith Act also includes a number of significant changes that affect the way patent applications will be prosecuted and also may affect patent litigation. These include allowing third party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent by USPTO administered post-grant proceedings, including post-grant review, *inter partes* review, and derivation proceedings. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in United States federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim unpatentable even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action. Accordingly, a third party may attempt to use the USPTO procedures to review patentability of our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action.

Therefore, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our owned or in-licensed patent applications and the enforcement or defense of our owned or in-licensed issued patents, all of which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

In addition, the patent positions of companies in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. As one example, in the case *Assoc. for Molecular Pathology v. Myriad Genetics, Inc.*, the U.S. Supreme Court held that certain claims to DNA molecules are not patentable simply because they have been isolated from surrounding material. Moreover, in 2012, the USPTO issued a guidance memo to patent examiners indicating that process claims directed to a law of nature, a natural phenomenon or a naturally occurring relation or correlation that do not include additional elements or steps that integrate the natural principle into the claimed invention such that the natural principle is practically applied and the claim amounts to significantly more than the natural principle itself should be rejected as directed to patent-ineligible subject matter. Accordingly, in view of the guidance memo, there can be no assurance that claims in our patent rights covering any therapeutic candidates we may develop or our technology will be held by the USPTO or equivalent foreign patent offices or by courts in the United States or in foreign jurisdictions to cover patentable subject matter. This combination of events has created uncertainty with respect to the validity and enforceability of patents once obtained. Depending on future actions by the U.S. Congress, the federal courts and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could have a material adverse effect on our patent rights and our ability to protect, defend and enforce our patent rights in the future.

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

Depending upon the timing, duration and specifics of any FDA marketing approval of any therapeutic candidates we may develop and our technology, one or more of our U.S. patents that we license or may own in the future may be eligible for limited patent term extension under Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent extension term of up to five years as compensation for patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent may be extended and only those claims covering the approved product, a method for using it or a method for manufacturing it may be extended. The application for the extension must be submitted prior to the expiration of the patent for which extension is sought and within 60 days of FDA approval. A patent that covers multiple products for which approval is sought can only be extended in connection with one of the approvals. However, we may not be granted an extension because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. In addition, to the extent we wish to pursue patent term extension based on a patent that we in-license from a third party, we would need the cooperation of that third party. If we are unable to obtain patent term extension or the term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

We may be subject to claims challenging the inventorship or ownership of our patent and other intellectual property rights.

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

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

In addition to seeking patent protection for our therapeutic programs and other proprietary technologies we may develop, we also rely on trade secrets and confidentiality agreements to protect our unpatented know-how, technology, and other proprietary information and to maintain our competitive position. With respect to our EEV Platform and development programs, we consider trade secrets and know-how to be one of our important sources of intellectual property, including our extensive knowledge of oligonucleotide drug delivery techniques and antibody conjugation. Trade secrets and know-how can be difficult to protect. In particular, the trade secrets and know-how in connection with our EEV Platform, development programs and other proprietary technology we may develop may over time be disseminated within the industry through independent development, the publication of journal articles describing the methodology and the movement of personnel with scientific positions in academic and industry.

We seek to protect these trade secrets and other proprietary technology, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, CROs, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. We cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology and processes. Despite 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 inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third party, our competitive position would be materially and adversely harmed.

We may be subject to claims that third parties have an ownership interest in our trade secrets. For example, we may have disputes arise from conflicting obligations of our employees, consultants or others who are involved in developing our therapeutic candidate. Litigation may be necessary to defend against these and other claims challenging ownership of our trade secrets. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable trade secret rights, such as exclusive ownership of, or right to use, trade secrets that are important to our therapeutic programs and other proprietary technologies we may develop. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to our management and other employees.

We may not be successful in obtaining necessary rights to any therapeutic candidate we may develop through acquisitions and in-licenses.

We currently own or exclusively license intellectual property rights covering certain aspects of our therapeutic programs. Other pharmaceutical companies and academic institutions may also have filed or are planning to file patent applications potentially relevant to our business. In order to avoid infringing these third-party patents, we may find it necessary or prudent to obtain licenses to such patents from such third-party intellectual property holders. However, we may be unable to secure such licenses or otherwise acquire or in-license any compositions, methods of use, processes or other intellectual property rights from third parties that we identify as necessary for our therapeutic programs and other proprietary technologies we may develop. The licensing or acquisition of third-party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third party intellectual property rights that we may consider attractive or necessary. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third party intellectual property rights on terms that would allow us to make an appropriate return on our investment or at all. If we are unable to successfully obtain rights to required third party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of the relevant program or therapeutic candidate, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

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

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

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

Third-party claims of intellectual property infringement, misappropriation or other violations against us or our collaborators may prevent or delay the development and commercialization of our therapeutic programs and other proprietary technologies we may develop.

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

Numerous U.S. and foreign issued patents and pending patent applications owned by third parties exist in the fields in which we are commercializing or plan to commercialize our therapeutic programs and in which we are developing other proprietary technologies. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our therapeutic programs and commercializing activities may give rise to claims of infringement of the patent rights of others. We are aware of third party patents that cover certain aspects of therapeutic candidates that we may develop. We cannot assure our stockholders that our therapeutic programs and other proprietary technologies we may develop will not infringe existing or future patents owned by third parties. We may not be aware of patents that have already been issued and that a third party, for example, a competitor in the fields in which we are developing our therapeutic programs, might assert as infringed by us. It is also possible that patents owned by third parties of which we are aware, but which we do not believe we infringe or that we believe we have valid defenses to any claims of patent infringement, could be found to be infringed by us. It is not unusual that corresponding patents issued in different countries have different scopes of coverage, such that in one country a third-party patent does not pose a material risk, but in another country, the corresponding third-party patent may pose a material risk to our planned products. As such, we review third-party patents in the relevant pharmaceutical markets. In addition, because patent applications can take many years to issue, there may be currently pending patent applications that may later result in issued patents that we may infringe.

In the event that any third party claims that we infringe their patents or that we are otherwise employing their proprietary technology without authorization and initiates litigation against us, even if we believe such claims are without merit, a court of competent jurisdiction could hold that such patents are valid, enforceable and infringed by us. In this case, the holders of such patents may be able to block our ability to commercialize the infringing products or technologies unless we obtain a license under the applicable patents, or until such patents expire or are finally determined to be held invalid or unenforceable. Such a license may not be available on commercially reasonable terms or at all. Even if we are able to obtain a license, the license would likely obligate us to pay license fees or royalties or both, and the rights granted to us might be

nonexclusive, which could result in our competitors gaining access to the same intellectual property. If we are unable to obtain a necessary license to a third-party patent on commercially reasonable terms, we may be unable to commercialize the infringing products or technologies or such commercialization efforts may be significantly delayed, which could in turn significantly harm our business.

Defense of infringement claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of management and other employee resources from our business, and may impact our reputation. In the event of a successful claim of infringement against us, we may be enjoined from further developing or commercializing the infringing products or technologies. In addition, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties and/or redesign our infringing products or technologies, which may be impossible or require substantial time and monetary expenditure. In that event, we would be unable to further develop and commercialize our therapeutic candidate or technologies, which could harm our business significantly. Further, we cannot predict whether any required license would be available at all or whether it would be available on commercially reasonable terms. In the event that we could not obtain a license, we may be unable to further develop our therapeutic candidate and commercialize our product, if approved, which could harm our business significantly. Even if we are able to obtain a license, the license would likely obligate us to pay license fees or royalties or both, and the rights granted to us might be nonexclusive, which could result in our competitors gaining access to the same intellectual property. Ultimately, we could be prevented from commercializing a product, or be forced to cease some aspect of our business operations, if, as a result of actual or threatened patent infringement claims, we are unable to enter into licenses on acceptable terms.

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

We may in the future pursue invalidity proceedings with respect to third-party patents. The outcome following legal assertions of invalidity is unpredictable. Even if resolved in our favor, these legal proceedings may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such proceedings adequately. Some of these third parties may be able to sustain the costs of such proceedings more effectively than we can because of their greater financial resources. If we do not prevail in the patent proceedings the third parties may assert a claim of patent infringement directed at our therapeutic candidates.

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

Third parties, such as a competitor, may infringe our patent rights. In an infringement proceeding, a court may decide that a patent owned by us is invalid or unenforceable or may refuse to stop the other party from using the invention at issue on the grounds that the patent does not cover the technology in question. In addition, our patent rights may become involved in inventorship, priority or validity disputes. To counter or defend against such claims can be expensive and time-consuming. An adverse result in any litigation proceeding could put our patent rights at risk of being invalidated or interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments, and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of

our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

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

Our registered or unregistered trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. During trademark registration proceedings, we may receive rejections of our applications by the USPTO or in other foreign jurisdictions. Although we are given an opportunity to respond to those rejections, we may be unable to overcome such rejections. In addition, in the USPTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, which may not survive such proceedings. Moreover, any name we have proposed to use with our therapeutic candidate in the United States must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. Similar requirements exist in Europe. The FDA typically conducts a review of proposed product names, including an evaluation of potential for confusion with other product names. If the FDA or an equivalent administrative body in a foreign jurisdiction objects to any of our proposed proprietary product names, we may be required to expend significant additional resources in an effort to identify a suitable substitute name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA or equivalent body. Furthermore, in many countries, owning and maintaining a trademark registration may not provide an adequate defense against a subsequent infringement claim asserted by the owner of a senior trademark.

We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors or other third parties may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks or trade names. Furthermore, assertions of potential trademark infringement or possible market confusion may lead to coexistence agreements in order to avoid costly disputes related to our trademarks. As a consequence, we may be forced to amend the list of goods and services covered by our trademarks more narrowly than as originally filed and intended, which could adversely affect our ability to establish name recognition. For example, the description of goods and services for our Entrada trademark was amended twice to settle potential disputes with two other biopharmaceutical companies as part of coexistence agreements. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade names, domain name or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely affect our business, financial condition, results of operations and prospects.

Intellectual property rights do not necessarily address all potential threats.

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

- others may be able to make products that are similar to our therapeutic candidate or utilize similar technology but that are not covered by the claims of the patents that we license or may own;
- we might not have been the first to make the inventions covered by our current or future patent applications;
- we might not have been the first to file patent applications covering our inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;

- it is possible that our current or future patent applications will not lead to issued patents;
- any patent issuing from our current or future patent applications may be held invalid or unenforceable, including as a result of legal challenges by our competitors or other third parties;
- our competitors or other third parties might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents of others may harm our business; and
- we may choose not to file for patent protection in order to maintain certain trade secrets or know-how, and a third party may subsequently file a patent application covering such intellectual property.

The occurrence of any of these events would have a material adverse effect on our business, financial condition, results of operations and prospects.

We partially depend on intellectual property licensed from third parties, and our licensors may not always act in our best interest. If we fail to comply with our obligations under our intellectual property licenses, if the licenses are terminated or if disputes regarding these licenses arise, we could lose significant rights that are important to our business.

We are dependent, in part, on patents, know-how and proprietary technology licensed from others. Our licenses to such patents, know-how and proprietary technology may not provide exclusive rights in all relevant fields of use and in all territories in which we may wish to develop or commercialize our therapeutics in the future. The agreements under which we license patents, know-how and proprietary technology from others are complex, and certain provisions in such agreements may be susceptible to multiple interpretations.

If we fail to comply with obligations under any license agreements, our licensors may have the right to terminate our license, in which event we would not be able to develop or market technology or therapeutic candidates covered by the intellectual property licensed under these agreements. In addition, we may need to obtain additional licenses from our existing licensors and others to advance our research or allow commercialization of therapeutic candidates we may develop. It is possible that we may be unable to obtain any additional licenses at a reasonable cost or on reasonable terms, if at all. In either event, we may be required to expend significant time and resources to redesign our technology, therapeutic candidates, or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize the affected technology or therapeutic candidates.

If we or our licensors fail to adequately protect our licensed intellectual property, our ability to commercialize therapeutic candidates could suffer. We do not have complete control over the maintenance, prosecution and litigation of our in-licensed patents and patent applications and may have limited control over future intellectual property that may be in-licensed. For example, we cannot be certain that activities such as the maintenance and prosecution by our licensors have been or will be conducted in compliance with applicable laws and regulations or will result in valid and enforceable patents and other intellectual property rights. It is possible that our licensors' infringement proceedings or defense activities may be less vigorous than had we conducted them ourselves, or may not be conducted in accordance with our best interests.

In addition, the resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant patents, know-how and proprietary technology, or increase what we believe to be our financial or other obligations under the relevant agreement. Disputes that may arise between us and our licensors regarding intellectual property subject to a license agreement could include disputes regarding:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- whether and the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;

- our right to sublicense patent and other rights to third parties under collaborative development relationships;
- our diligence obligations with respect to the use of the licensed technology in relation to our development and commercialization of our therapeutic candidates and what activities satisfy those diligence obligations; and
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected technology or therapeutic candidates. As a result, any termination of or disputes over our intellectual property licenses could result in the loss of our ability to develop and commercialize our EEV Platform, or EEV products, or we could lose other significant rights, any of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

For example, our agreements with certain of our third-party research partners provide that improvements developed in the course of our relationship may be owned solely by either us or our third-party research partner, or jointly between us and the third party. If we determine that rights to such improvements owned solely by a research partner or other third party with whom we collaborate are necessary to commercialize our therapeutic candidates or maintain our competitive advantage, we may need to obtain a license from such third party in order to use the improvements and continue developing, manufacturing or marketing our therapeutic candidates. We may not be able to obtain such a license on an exclusive basis, on commercially reasonable terms, or at all, which could prevent us from commercializing our therapeutic candidates or allow our competitors or others the chance to access technology that is important to our business. We also may need the cooperation of any co-owners of our intellectual property in order to enforce such intellectual property against third parties, and such cooperation may not be provided to us.

We may not be successful in obtaining or maintaining necessary rights to product components and processes for our development portfolio through acquisitions and in-licenses.

The growth of our business may depend in part on our ability to acquire, in-license or use third-party proprietary rights. For example, our therapeutic candidates may require specific formulations to work effectively and efficiently, we may develop therapeutic candidates containing our compounds and pre-existing pharmaceutical compounds, or we may be required by the FDA or comparable foreign regulatory authorities to provide a companion diagnostic test or tests with our therapeutic candidates, any of which could require us to obtain rights to use intellectual property held by third parties. In addition, with respect to any patents we may co-own with third parties, we may require licenses to such co-owners interest to such patents. We may be unable to acquire or in-license any compositions, methods of use, processes or other third-party intellectual property rights from third parties that we identify as necessary or important to our business operations. In addition, we may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. Were that to happen, we may need to cease use of the compositions or methods covered by those third-party intellectual property rights, and may need to seek to develop alternative approaches that do not infringe on those intellectual property rights, which may entail additional costs and development delays, even if we were able to develop such alternatives, which may not be feasible. Even if we are able to obtain a license, it may be non-exclusive, which means that our competitors may also receive access to the same technologies licensed to us. In that event, we may be required to expend significant time and resources to develop or license replacement technology.

Additionally, we sometimes collaborate with academic institutions to accelerate our preclinical research or development under written agreements with these institutions. In certain cases, these institutions provide us with an option to negotiate a license to any of the institution’s rights in technology resulting from the collaboration. Even if we hold such an option, we may be unable to negotiate a license from the institution within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to others, potentially blocking our ability to pursue our program.

The licensing and acquisition of third-party intellectual property rights is a competitive area, and companies that may be more established or have greater resources than we do may also be pursuing strategies to license or acquire third-party intellectual property rights that we may consider necessary or attractive in order to commercialize our therapeutic candidates. More established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor

may be unwilling to assign or license rights to us. There can be no assurance that we will be able to successfully complete these types of negotiations and ultimately acquire the rights to the intellectual property surrounding the additional therapeutic candidates that we may seek to develop or market. If we are unable to successfully obtain rights to required third-party intellectual property or to maintain the existing intellectual property rights we have, we may have to abandon development of certain programs and our business financial condition, results of operations and prospects could suffer.

We, our collaborators and our service providers may be subject to a variety of privacy and data security laws and contractual obligations, which could increase compliance costs and our failure to comply with them could subject us to potentially significant fines or penalties and otherwise harm our business.

We maintain a large quantity of sensitive information, including confidential business and patient health information in connection with our preclinical studies, and are subject to laws and regulations governing the privacy and security of such information. The global data protection landscape is rapidly evolving, and we may be affected by or subject to new, amended or existing laws and regulations in the future, including as our operations continue to expand or if we operate in foreign jurisdictions. These laws and regulations may be subject to differing interpretations, which adds to the complexity of processing personal data. Guidance on implementation and compliance practices are often updated or otherwise revised.

In the United States, there are numerous federal and state privacy and data security laws and regulations governing the collection, use, disclosure and protection of personal information, including federal and state health information privacy laws, federal and state security breach notification laws and federal and state consumer protection laws. Each of these laws is subject to varying interpretations and constantly evolving. By way of example, HIPAA imposes privacy and security requirements and breach reporting obligations with respect to individually identifiable health information upon “covered entities” (health plans, health care clearinghouses and certain health care providers), and their respective business associates, individuals or entities that create, received, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity. HIPAA mandates the reporting of certain breaches of health information to the U.S. Department of Health and Human Services (HHS), affected individuals and if the breach is large enough, the media. Entities that are found to be in violation of HIPAA may be subject to significant civil, criminal and administrative fines and penalties and/or additional reporting and oversight obligations. Even when HIPAA does not apply, failing to take appropriate steps to keep consumers’ personal information secure may constitute unfair acts or practices in or affecting commerce in violation of Section 5(a) of the Federal Trade Commission Act (FTCA), 15 U.S.C § 45(a). The FTC expects a company’s data security measures to be reasonable and appropriate in light of the sensitivity and volume of consumer information it holds, the size and complexity of its business and the cost of available tools to improve security and reduce vulnerabilities. Individually identifiable health information is considered sensitive data that merits stronger safeguards.

In addition, certain state laws govern the privacy and security of health information in certain circumstances, some of which are more stringent than HIPAA and many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. By way of example, the California Consumer Privacy Act (CCPA), which went into effect on January 1, 2020, gives California residents expanded rights to access and delete their personal information, opt out of certain personal information sharing, and receive detailed information about how their personal information is used. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation. The CCPA may increase our compliance costs and potential liability. Some observers have noted that the CCPA could mark the beginning of a trend toward more stringent privacy legislation in the United States, which could increase our potential liability and adversely affect our business.

Further, a new California privacy law, the California Privacy Rights Act (CPRA), was passed by California voters on November 3, 2020. The CPRA will create additional obligations with respect to processing and storing personal information that are scheduled to take effect on January 1, 2023 (with certain provisions having retroactive effect to January 1, 2022). Additionally, some observers have noted that the CCPA and CPRA could mark the beginning of a trend toward more stringent privacy legislation in the U.S., which could increase our potential liability and adversely affect our business. Already, in the United States, we have witnessed significant developments at the state level. For example, on March 2, 2021, Virginia enacted the Consumer Data Protection Act (CDPA) and, on July 8, 2021, Colorado’s governor signed the Colorado Privacy Act (CPA), into law. The CDPA and the CPA will both become effective January 1, 2023. While the CDPA and CPA incorporate many similar concepts of the CCPA and CPRA, there are also several key differences in the scope, application, and enforcement of the law that will change the operational practices of regulated businesses. The new laws will, among other things, impact how regulated businesses collect and

process personal sensitive data, conduct data protection assessments, transfer personal data to affiliates, and respond to consumer rights requests.

A number of other states have proposed new privacy laws, some of which are similar to the above discussed recently passed laws. Such proposed legislation, if enacted, may add additional complexity, variation in requirements, restrictions and potential legal risk, require additional investment of resources in compliance programs, impact strategies and the availability of previously useful data and could result in increased compliance costs and/or changes in business practices and policies. The existence of comprehensive privacy laws in different states in the country would make our compliance obligations more complex and costly and may increase the likelihood that we may be subject to enforcement actions or otherwise incur liability for noncompliance.

In the EU, on May 25 2018, a new privacy regime, the General Data Protection Regulation, the GDPR, took effect in the European Economic Area (EEA). The GDPR governs the collection, use, disclosure, transfer or other processing of personal data of European persons. Among other things, the GDPR imposes new requirements regarding the security of personal data and notification of data processing obligations to the competent national data processing authorities, changes the lawful bases on which personal data can be processed, expands the definition of personal data and requires changes to informed consent practices, as well as more detailed notices for clinical trial subjects and investigators. In addition, the GDPR increases the scrutiny of transfers of personal data from clinical trial sites located in the EEA to the United States and other jurisdictions that the European Commission does not recognize as having "adequate" data protection laws, and imposes substantial fines for breaches and violations (up to the greater of €20 million or 4% of our consolidated annual worldwide gross revenue). The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies and obtain compensation for damages resulting from violations of the GDPR. Moreover, the United Kingdom leaving the EU could also lead to further legislative and regulatory changes. In addition, further to the U.K.'s exit from the EU on January 31, 2020, the GDPR ceased to apply in the U.K. at the end of the transition period on December 31, 2020. However, as of January 1, 2021, the U.K.'s European Union (Withdrawal) Act 2018 incorporated the U.K. GDPR into U.K. law. The U.K. GDPR and the U.K. Data Protection Act 2018 set out the U.K.'s data protection regime, which is independent from but aligned to the EU's data protection regime. Non-compliance with the U.K. GDPR may result in monetary penalties of up to £17.5 million or 4% of worldwide revenue, whichever is higher. Although the UK is regarded as a third country under the EU's GDPR, the European Commission (EC) has now issued a decision recognizing the UK as providing adequate protection under the EU GDPR and, therefore, transfers of personal data originating in the EU to the UK remain unrestricted. Like the EU GDPR, the UK GDPR restricts personal data transfers outside the UK to countries not regarded by the UK as providing adequate protection. The UK government has confirmed that personal data transfers from the UK to the EEA remain free flowing.

To enable the transfer of personal data outside of the EEA or the UK, adequate safeguards must be implemented in compliance with European and UK data protection laws. On June 4, 2021, the EC issued new forms of standard contractual clauses for data transfers from controllers or processors in the EU/EEA (or otherwise subject to the GDPR) to controllers or processors established outside the EU/EEA (and not subject to the GDPR). The new standard contractual clauses replace the standard contractual clauses that were adopted previously under the EU Data Protection Directive. The UK is not subject to the EC's new standard contractual clauses but has published a draft version of a UK-specific transfer mechanism, which, once finalized, will enable transfers from the UK. We will be required to implement these new safeguards when conducting restricted data transfers under the EU and UK GDPR and doing so will require significant effort and cost.

Compliance with these and any other applicable privacy and data security laws and regulations is a rigorous and time-intensive process, and we may be required to put in place additional mechanisms ensuring compliance with the new data protection rules. If we fail to comply with any such laws or regulations, we may face significant fines and penalties that could adversely affect our business, financial condition and results of operations.

Use of open source software could impose limitations on us that may adversely affect our business.

Should use of open source software be necessary for commercialization of our therapeutic candidates, such use could impose limitations on our ability to commercialize. As a result, as we seek to use our platform in connection with commercially available products, we may be required to license software under different license terms, which may not be possible on commercially reasonable terms, if at all. If we are unable to license software components on terms that permit its use for commercial purposes, we may be required to replace those software components, which could result in delays, additional cost and additional regulatory approvals.

Use and distribution of open source software may entail greater risks than use of third-party commercial software, as open source licensors generally do not provide warranties or other contractual protections regarding infringement claims or the quality of the software code. Some open source licenses contain requirements that we make available source code for modifications or derivative works we create based upon the type of open source software we use. If we combine our proprietary software with open source software in a certain manner, we could, under certain of the open source licenses, be required to release the source code of our proprietary software to the public. This could allow our competitors to create similar products with lower development effort and time, and ultimately could result in a loss of product sales for us. Although we monitor our use of open source software, the terms of many open source licenses have not been interpreted by U.S. courts, and there is a risk that those licenses could be construed in a manner that could impose unanticipated conditions or restrictions on our ability to commercialize our therapeutic candidates. We could be required to seek licenses from third parties in order to continue offering our therapeutic candidates, to re-engineer our therapeutic candidates or to discontinue the sale of our therapeutic candidates in the event re-engineering cannot be accomplished on a timely basis, any of which could materially and adversely affect our business, financial condition, results of operations and prospects.

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

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor or other third party will discover our trade secrets or that our trade secrets will be misappropriated or disclosed.

Because we currently rely on certain third parties to manufacture all or part of our drug product and to perform quality testing, and because we collaborate with various organizations and academic institutions for the advancement of our product engine and development portfolio, we must, at times, share our proprietary technology and confidential information, including trade secrets, with them. We seek to protect our proprietary technology, in part, by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements and other similar agreements with our collaborators, advisors, employees, consultants and contractors prior to beginning research or disclosing any proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, including our trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors or other third parties, are inadvertently incorporated into the technology of others or are disclosed or used in violation of these agreements. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of these agreements, independent development or publication of information including our trade secrets by third parties. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's or other third party's discovery of our proprietary technology and confidential information or other unauthorized use or disclosure would impair our competitive position and may harm our business, financial condition, results of operations and prospects.

Rights to improvements to our therapeutic candidates may be held by third parties.

In the course of testing our therapeutic candidates, we may enter into agreements with third parties to conduct clinical testing, which may provide that improvements to our therapeutic candidates may be owned solely by a party or jointly between the parties. If we determine that rights to such improvements owned solely by a third party are necessary to commercialize our therapeutic candidates or maintain our competitive advantage, we may need to obtain a license from such third party in order to use the improvements and continue developing, manufacturing or marketing the therapeutic candidates. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain such a license, it could be granted on non-exclusive terms, thereby giving our competitors and other third parties access to the same technologies licensed to us. Failure to obtain a license on commercially reasonable terms or at all, or to obtain an exclusive license, could prevent us from commercializing our therapeutic candidates or force us to cease some of our business operations, which could materially harm our business. If we determine that rights to improvements jointly owned between us and a third party are necessary to commercialize our therapeutic candidates or maintain our competitive advantage, we may need to obtain an exclusive license from such third party. If we are unable to obtain an exclusive license to any such third-party co-owners' interest in such improvements, such co-owners may be able to license their rights to other third parties, including our competitors, and our competitors could market competing products and technology. In addition, we may need the cooperation of any such co-owners of our intellectual property in order to enforce such intellectual property against third parties, and such cooperation may not be provided to us. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

We may be subject to claims that we have wrongfully hired an employee from a competitor or that we or our employees have wrongfully used or disclosed alleged confidential information or trade secrets of their former employers.

As is common in the biotechnology and pharmaceutical industries, in addition to our employees, we engage the services of consultants to assist us in the development of our therapeutic candidate, and other proprietary technologies. Many of these consultants, and many of our employees, were previously employed at, or may have previously provided or may be currently providing consulting services to, other pharmaceutical companies including our competitors or potential competitors. We may become subject to claims that we, our employees or a consultant inadvertently or otherwise used or disclosed trade secrets or other information proprietary to their former employers or their former or current clients. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could adversely affect our business. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to our management team and other employees.

Risks Related to Ownership of Our Common Stock

We do not know whether an active, liquid and orderly trading market will develop for our common stock and as a result it may be difficult for our stockholders to sell their shares of our common stock.

Prior to our initial public offering, no market for shares of our common stock existed and an active trading market for our shares may never develop or be sustained. The lack of an active market may impair our stockholders' ability to sell their shares at the time they wish to sell them or at a price that they consider reasonable. The lack of an active market may also reduce the fair market value of our stockholders' shares. Furthermore, an inactive market may also impair our ability to raise capital by selling shares of our common stock and may impair our ability to enter into strategic collaborations or acquire companies, technologies or other assets by using our shares of common stock as consideration.

The market price of our common stock may be volatile, and investors could lose all or part of their investment.

The trading price of our common stock is likely to be highly volatile and subject to wide fluctuations in response to various factors, some of which we cannot control. The stock market in general, and pharmaceutical and biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies.

Broad market and industry factors may negatively affect the market price of our common stock, regardless of our actual operating performance. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this Annual Report, these factors include:

- the timing and results of INDs, preclinical studies and clinical trials of our therapeutic candidates or those of our competitors;
- the success of competitive products or announcements by potential competitors of their product development efforts;
- our decision to initiate a clinical trial, not to initiate a clinical trial or to terminate an existing clinical trial;
- any delay in our regulatory filings for our therapeutic candidates and any adverse development or perceived adverse development with respect to the applicable regulatory authority's review of such filings;
- adverse developments concerning our potential future in-house manufacturing facilities or CMOs;
- regulatory actions with respect to our therapeutics or therapeutic candidates or our competitors' products or therapeutic candidates;
- actual or anticipated changes in our growth rate relative to our competitors;
- the size and growth of our initial target markets;

- unanticipated serious safety concerns related to the use of our therapeutic candidates;
- regulatory or legal developments in the U.S. and other countries;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- significant lawsuits, including patent or stockholder litigation;
- publication of research reports about us or our industry, or positive or negative recommendations or withdrawal of research coverage by securities analysts;
- the recruitment or departure of key personnel;
- announcements by us or our competitors of significant acquisitions, strategic collaborations, joint ventures, collaborations or capital commitments;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- market conditions in the pharmaceutical and biotechnology sector;
- changes in the structure of healthcare payment systems;
- share price and volume fluctuations attributable to inconsistent trading volume levels of our shares;
- our failure to meet the estimates and projections of the investment community or that we may otherwise provide to the public;
- announcement or expectation of additional financing efforts;
- sales of our common stock by us, our insiders or our other stockholders;
- expiration of market stand-off or lock-up agreements;
- the impact of any natural disasters or public health emergencies, such as the ongoing COVID-19 pandemic;
- general economic, political, industry and market conditions; and
- other events or factors, many of which are beyond our control.

The realization of any of the above risks or any of a broad range of other risks, including those described in this "Risk factors" section, could have a dramatic and adverse impact on the market price of our common stock.

If securities or industry analysts do not publish research or reports, or if they publish adverse or misleading research or reports, regarding us, our business or our market, our stock price and trading volume could decline.

The trading market for our common stock will be influenced by the research and reports that securities or industry analysts publish about us, our business or our market. In the event that one or more of the analysts who covers us issues adverse or misleading research or reports regarding us, our business model, our intellectual property, our stock performance or our market, or if our operating results fail to meet the expectations of analysts, our stock price would likely decline. If one or more of these analysts cease coverage of us or fail to publish reports on us regularly, we could lose visibility in the financial markets, which in turn could cause our stock price or trading volume to decline.

Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and stock price.

As widely reported, global credit and financial markets have experienced extreme volatility and disruptions in the past several years, most recently due to the evolving ongoing COVID-19 pandemic, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions, whether due to the evolving effects of the COVID-19 pandemic or otherwise, will not occur. Our general business strategy may be adversely affected by any such economic downturn, volatile business environment or continued unpredictable and unstable market conditions. If the current equity and credit markets deteriorate, or do not improve, it may make any necessary debt or equity financing more difficult, more costly, and more dilutive.

Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse event on our growth strategy, financial performance and stock price and could require us to delay or abandon clinical development plans. In addition, there is a risk that one or more of our current service providers, manufacturers and other partners may not survive these difficult economic times, which could directly affect our ability to attain our operating goals on schedule and on budget.

Our stock price may decline due in part to the volatility of the stock market and the general economic downturn.

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

Our executive officers, directors, holders of 5% or more of our capital stock and their respective affiliates beneficially owned approximately 87.4% of our outstanding voting stock as of December 31, 2021. These stockholders, acting together, may be able to impact matters requiring stockholder approval. For example, they may be able to impact elections of directors, amendments of our organizational documents or approval of any merger, sale of assets or other major corporate transaction. This may prevent or discourage unsolicited acquisition proposals or offers for our common stock that investors may feel are in their best interest as one of our stockholders. The interests of this group of stockholders may not always coincide with each investor's interests or the interests of other stockholders and they may act in a manner that advances their best interests and not necessarily those of other stockholders, including seeking a premium value for their common stock, and might affect the prevailing market price for our common stock.

Future sales and issuances of our common stock or rights to purchase common stock, including pursuant to our 2021 Plan, could result in additional dilution of the percentage ownership of our stockholders and could cause our stock price to fall.

We expect that significant additional capital may be needed in the future to continue our planned operations, including conducting clinical trials, commercialization efforts, expanded research and development activities and costs associated with operating a public company. To raise capital, we may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. If we sell common stock, convertible securities or other equity securities, investors may be materially diluted by subsequent sales. Such sales may also result in material dilution to our existing stockholders, and new investors could gain rights, preferences and privileges senior to the holders of our common stock.

Pursuant to our 2021 Plan, our management is authorized to grant stock options to our employees, directors and consultants. If the number of shares reserved under our 2021 Plan is increased pursuant to the terms of the 2021 Plan, our stockholders may experience additional dilution, which could cause our stock price to fall.

Any of the above events could significantly harm our business, prospects, financial condition and results of operations and cause the price of our common stock to decline.

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

We do not have any committed external source of funds or other support for our development and commercialization efforts, and we cannot be certain that additional funding will be available on acceptable terms, or at all.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through equity offerings, debt financings, or other capital sources, including potential collaborations, licenses and other similar arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, our stockholders' ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect our stockholders' rights. Any future 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, selling or licensing our assets, making capital expenditures, declaring dividends or encumbering our assets to secure future indebtedness. Such restrictions could adversely impact our ability to conduct our operations and execute our business plan.

As a result of our recurring losses from operations and recurring negative cash flows from operations, there is uncertainty regarding our ability to maintain liquidity sufficient to operate our business effectively. If we raise additional funds through future collaborations, licenses and other similar arrangements, we may have to relinquish valuable rights to our future revenue streams, research programs, therapeutic candidates or EEV Platform, or grant licenses on terms that may not be favorable to us and/or that may reduce the value of our common stock. If we are unable to raise additional funds through equity or debt financings or other arrangements when needed or on terms acceptable to us, we would be required to delay, limit, reduce, or terminate our product development or future commercialization efforts or grant rights to develop and market therapeutic candidates that we would otherwise prefer to develop and market ourselves. Any of the above events could significantly harm our business, prospects, financial condition and results of operations and cause the price of our common stock to decline.

We are an "emerging growth company" and a smaller reporting company, and we cannot be certain if the reduced reporting requirements applicable to emerging growth companies and smaller reporting companies will make our common stock less attractive to investors.

We are an "emerging growth company," as defined in the Jumpstart Our Business Startups Act of 2012 (JOBS Act). For as long as we continue to be an emerging growth company, we intend to take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies, including:

- being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure in our periodic reports;
- not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, as amended (Sarbanes-Oxley Act);
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements; and
- exemptions from the requirements of holding nonbinding advisory stockholder votes on executive compensation and stockholder approval of any golden parachute payments not previously approved.

Under the JOBS Act, emerging growth companies can also delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have elected to avail ourselves of this exemption from new or revised accounting standards and, therefore, will not be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies. As a result, our financial statements may not be comparable to companies that comply with the new or revised accounting pronouncements as of public company effective dates.

We will remain an emerging growth company until the earliest to occur of: (i) the last day of the fiscal year in which we have more than $1.07 billion in annual revenue; (ii) the date we qualify as a "large accelerated filer," with at least $700.0 million of equity securities held by non-affiliates; (iii) the date on which we have issued more than $1.0 billion in

non-convertible debt securities during the prior three-year period; and (iv) the last day of the fiscal year ending after the fifth anniversary of our initial public offering.

Even after we no longer qualify as an emerging growth company, we may still qualify as a "smaller reporting company," which would allow us to continue to take advantage of many of the same exemptions from disclosure requirements, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions.

We do not intend to pay dividends on our common stock so any returns will be limited to the value of our stock.

We have never declared or paid any cash dividends on our common stock. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to any appreciation in the value of their stock.

Anti-takeover provisions in our certificate of incorporation, our bylaws and Delaware law might discourage, delay or prevent a change in control of our company or changes in our management and, therefore, depress the market price of our common stock.

Our fourth amended and restated certificate of incorporation and amended and restated bylaws contain provisions that could depress the market price of our common stock by acting to discourage, delay or prevent a change in control of our company or changes in our management that the stockholders of our company may deem advantageous. These provisions include, among other things:

- a board of directors divided into three classes serving staggered three-year terms, such that not all members of the board will be elected at one time;
- a prohibition on stockholder actions through written consent, which requires that all stockholder actions be taken at a meeting of our stockholders;
- a requirement that special meetings of stockholders be called only by the board of directors acting pursuant to a resolution approved by the affirmative vote of a majority of the directors then in office;
- advance notice requirements for stockholder proposals and nominations for election to our board of directors;
- a requirement that no member of our board of directors may be removed from office by our stockholders except for cause and, in addition to any other vote required by law, upon the approval of not less than two-thirds of all outstanding shares of our voting stock then entitled to vote in the election of directors;
- a requirement of approval of not less than two-thirds of all outstanding shares of our voting stock to amend any bylaws by stockholder action;
- a requirement of approval by the affirmative vote of a majority of the outstanding shares of our voting stock to amend or repeal specified provisions of our certificate of incorporation, and the affirmative vote of a majority of the outstanding shares of each class entitled to vote thereon as a class, at a duly constituted meeting of stockholders called expressly for such purpose; and
- the authority of the board of directors to issue preferred stock on terms determined by the board of directors without stockholder approval and which preferred stock may include rights superior to the rights of the holders of common stock.

In addition, Section 203 of the General Corporation Law of the State of Delaware (DGCL) prohibits a publicly-held Delaware corporation from engaging in a business combination with an interested stockholder, generally a person which together with its affiliates owns, or within the last three years has owned, 15% of our voting stock, for a period of three years after the date of the transaction in which the person became an interested stockholder, unless the business combination is approved in a prescribed manner.

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

Our bylaws designate certain courts as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers, or employees.

Our amended and restated bylaws provide that, unless we consent in writing to an alternative forum, the Court of Chancery of the State of Delaware is the sole and exclusive forum for any state law claims for (i) any derivative action or proceeding brought on our behalf, (ii) any action asserting a claim of breach of, or a claim based on, fiduciary duty owed by any of our current or former directors, officers, and employees to us or our stockholders, (iii) any action asserting a claim arising pursuant to any provision of the Delaware General Corporation Law, our certificate of incorporation or our bylaws or (iv) any action asserting a claim that is governed by the internal affairs doctrine, in each case subject to the Court of Chancery having personal jurisdiction over the indispensable parties named as defendants therein (Delaware Forum Provision). The Delaware Forum Provision will not apply to any causes of action arising under the Securities Act or the Exchange Act. Our amended and restated bylaws further provide that, unless we consent in writing to the selection of an alternative forum, the federal district courts of the U.S. shall be the sole and exclusive forum for resolving any complaint asserting a cause or causes of action arising under the Securities Act (Federal Forum Provision). In addition, our amended and restated bylaws provide that any person or entity purchasing or otherwise acquiring any interest in shares of our common stock is deemed to have notice of and consented to the foregoing provisions; provided, however, that stockholders cannot and will not be deemed to have waived our compliance with the federal securities laws and the rules and regulations thereunder.

The Delaware Forum Provision and the Federal Forum Provision in our amended and restated bylaws may impose additional litigation costs on stockholders in pursuing any such claims. Additionally, the forum selection clauses in our amended and restated bylaws may limit our stockholders' ability to bring a claim in a forum that they find favorable for disputes with us or our directors, officers or employees, which may discourage such lawsuits against us and our directors, officers and employees even though an action, if successful, might benefit our stockholders. In addition, while the Delaware Supreme Court ruled in March 2020 that federal forum selection provisions purporting to require claims under the Securities Act be brought in federal court were "facially valid" under Delaware law, there is uncertainty as to whether other courts will enforce our Federal Forum Provision. If the Federal Forum Provision is found to be unenforceable, we may incur additional costs associated with resolving such matters. The Federal Forum Provision may also impose additional litigation costs on stockholders who assert that the provision is not enforceable or invalid. The Court of Chancery of the State of Delaware and the federal district courts of the U.S. may also reach different judgments or results than would other courts, including courts where a stockholder considering an action may be located or would otherwise choose to bring the action, and such judgments may be more or less favorable to us than our stockholders.

Our failure to meet Nasdaq's continued listing requirements could result in a delisting of our common stock.

If we fail to satisfy Nasdaq's continued listing requirements, such as the corporate governance requirements or the minimum closing bid price requirement, Nasdaq may take steps to delist our common stock. Such a delisting would likely have a negative effect on the price of our common stock and would impair our stockholders' ability to sell or purchase our common stock when our stockholders wish to do so. In the event of a delisting, we can provide no assurance that any action taken by us to restore compliance with listing requirements would allow our common stock to become listed again, stabilize the market price or improve the liquidity of our common stock, prevent our common stock from dropping below the Nasdaq minimum bid price requirement or prevent future non-compliance with Nasdaq's listing requirements.

General Risk Factors

We will incur increased costs as a result of operating as a public company, and our management will devote substantial time to related compliance initiatives.

As a public company, we will incur significant legal, accounting and other expenses that we did not incur as a private company, and these expenses may increase even more after we are no longer an "emerging growth company." We are subject to the reporting requirements of the Securities Exchange Act of 1934, as amended (Exchange Act), the Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Protection Act, as well as rules adopted, and to be adopted, by the SEC and Nasdaq. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, we expect these rules and regulations to substantially increase our legal and financial compliance costs and to make some activities more time-consuming and costly, which will increase our operating expenses. For example, we expect these rules and regulations to make it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to incur substantial costs to maintain sufficient coverage, particularly in light of recent cost increases related to coverage. We cannot accurately predict or estimate the amount or timing of additional costs we may incur to respond to these requirements. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers.

In addition, as a public company we will be required to incur additional costs and obligations in order to comply with SEC rules that implement Section 404 of the Sarbanes-Oxley Act. Under these rules, beginning with our second annual report on Form 10-K after we become a public company, we will be required to make a formal assessment of the effectiveness of our internal control over financial reporting, and once we cease to be an emerging growth company, we may be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we will be engaging in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of our internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are designed and operating effectively, and implement a continuous reporting and improvement process for internal control over financial reporting.

If we experience material weaknesses in the future or otherwise fail to maintain an effective system of internal controls in the future, we may not be able to accurately or timely report our financial condition or results of operations, which may adversely affect investor confidence in us and, as a result, the value of our common stock.

We may in the future discover material weaknesses in our system of internal financial and accounting controls and procedures that could result in a material misstatement of our financial statements. Our internal control over financial reporting will not prevent or detect all errors and all fraud. A control system, no matter how well designed and operated, can provide only reasonable, not absolute, assurance that the control system's objectives will be met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that misstatements due to error or fraud will not occur or that all control issues and instances of fraud will be detected.

We, and our independent registered public accounting firm, were not required to perform an evaluation of our internal control over financial reporting as of December 31, 2021 in accordance with the provisions of the Sarbanes-Oxley Act. Accordingly, we cannot assure our stockholders that we will not in the future identify material weaknesses. Material weaknesses may exist when we become required to report on the effectiveness of our internal control over financial reporting under Section 404 of the Sarbanes-Oxley Act.

If we are not able to comply with the requirements of Section 404 of the Sarbanes-Oxley Act in a timely manner, or if we are unable to maintain proper and effective internal controls over financial reporting, we may not be able to produce timely and accurate financial statements. If that were to happen, our investors could lose confidence in our reported financial information, the market price of our stock could decline, and we could be subject to sanctions or investigations by the stock exchange on which our common stock is listed, the SEC or other regulatory authorities.

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

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

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

We may be subject to securities litigation, which is expensive and could divert management attention.

The market price of our common stock may be volatile and, in the past, companies that have experienced volatility in the market price of their stock have been subject to securities class action litigation. We may be the target of this type of litigation in the future. Securities litigation against us could result in substantial costs and divert our management's attention from other business concerns, which could seriously harm our business.

Our insurance policies are expensive and only protect us from some business risks, which will leave us exposed to significant uninsured liabilities.

We do not carry insurance for all categories of risk that our business may encounter. Some of the policies we currently maintain include property, general liability, employment benefits liability, business automobile, workers' compensation, and directors' and officers', employment practices and fiduciary liability insurance. We do not know, however, if we will be able to maintain insurance with adequate levels of coverage. Any significant uninsured liability may require us to pay substantial amounts, which would adversely affect our financial position and results of operations.

Disruptions at the FDA and other government agencies caused by funding shortages or global health concerns could hinder their ability to hire, retain or deploy key leadership and other personnel, or otherwise prevent new or modified products from being developed, approved or commercialized in a timely manner or at all, 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, statutory, regulatory and policy changes, the FDA's ability to hire and retain key personnel and accept the payment of user fees, and other events that may otherwise affect the FDA's ability to perform routine functions. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of other government agencies 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 and biologics or modifications to approved drugs and biologics to be reviewed and/or approved by necessary government agencies, which would adversely affect our business.

Most recently, the ongoing COVID-19 pandemic created a shortage of available resources at the FDA. Since March 2020 when foreign and domestic inspections of facilities were largely placed on hold, the FDA has been working to resume routine surveillance, bioresearch monitoring and pre-approval inspections on a prioritized basis. Since April 2021, the FDA has conducted limited inspections and employed remote interactive evaluations, using risk management methods, to meet user fee commitments and goal dates. Ongoing travel restrictions and other uncertainties continue to impact oversight operations both domestic and abroad and it is unclear when standard operational levels will resume. The FDA is continuing to complete mission-critical work, prioritize other higher-tiered inspectional needs (e.g., for-cause inspections), and carry out surveillance inspections using risk-based approaches for evaluating public health. Should the FDA determine that an inspection is necessary for approval and an inspection cannot be completed during the review cycle due to restrictions on travel, and the FDA does not determine a remote interactive evaluation to be adequate, the agency has stated that it generally intends to issue, depending on the circumstances, a complete response letter or defer action on the application until an inspection can be completed. During the COVID-19 pandemic, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications.

Additionally, during the COVID-19 pandemic, the FDA has stated that it is working to ensure timely reviews of applications for medical products in line with its user fee performance goals. However, the FDA may not be able to continue its current pace and approval timelines could be extended, including where a pre-approval inspection or an inspection of clinical sites is required and due to the ongoing COVID-19 pandemic and travel restrictions, the FDA is unable to complete such required inspections during the review period.

Regulatory authorities outside the United States may adopt similar restrictions or other policy measures in response to the ongoing COVID-19 pandemic and may experience delays in their regulatory activities. If a prolonged government shutdown occurs, or if global health concerns continue to prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities, including formal and informal interactions with product developers, it could significantly impact the ability of the FDA or other regulatory authorities to timely review and process our future regulatory submissions, which could have a material adverse effect on our business.

Item 1B. Unresolved Staff Comments

Not applicable.

Item 2. Properties

Our corporate headquarters are located in Boston, Massachusetts, where we lease a facility containing approximately 34,866 square feet of office, research and development and laboratory space. The lease expires on November 30, 2025, subject to an option to terminate the lease after November 30, 2023 without penalty or to extend for three additional years.

We believe our facilities are adequate and suitable for our current needs and that should it be needed, suitable additional or alternative space at commercially reasonable terms will be available as needed to accommodate any future expansion of our operations.

Item 3. Legal Proceedings

From time to time, we may become involved in litigation or other legal proceedings arising in the ordinary course of our business. While the outcome of any such proceedings cannot be predicted with certainty, as of December 31, 2021, we were not a party to any litigation or legal proceedings that, in the opinion of our management, are probable to have a material adverse effect on our business. Regardless of outcome, litigation can have an adverse impact on our business, financial condition, results of operations and prospects because of defense and settlement costs, diversion of management resources and other factors.

Item 4. Mine Safety Disclosures

Not applicable.

PART II

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

Market Information

Our common stock has traded on the Nasdaq Global Market under the symbol "TRDA" since October 29, 2021. Prior to that date, there was no public trading market for our common stock.

Holders of Our Common Stock

As of February 28, 2022, there were approximately 65 stockholders of record of our common stock. The actual number of stockholders is greater than the number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees. The number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Dividends

We have never declared or paid any cash dividends on our common stock. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future.

Securities Authorized for Issuance Under Equity Compensation Plans

The information required by Item 5 of Form 10-K regarding equity compensation plans is incorporated herein by reference to Item 12 of Part III of this Annual Report.

Recent Sales of Unregistered Equity Securities

The information required by Item 701 of Regulation S-K was previously included in Quarterly Report on Form 10-Q filed on December 9, 2021 (File No. 001-40969).

Use of Proceeds from our Initial Public Offering of Common Stock

In November 2021, the Company completed its initial public offering (IPO) in which the Company issued and sold 10,436,250 shares of its common stock, including 1,361,250 shares pursuant to the full exercise of the underwriters' option to purchase additional shares, at a public offering price of $20.00 per share. All of the shares of common stock issued and sold in our IPO were registered under the Securities Act pursuant to a registration statement on Form S-1, as amended (File No. 333-260160), which was declared effective by the Securities and Exchange Commission (the SEC) on October 28, 2021. Goldman Sachs & Co. LLC, Cowen and Company, LLC and Evercore Group L.L.C. acted as joint book-running managers for the offering.

The aggregate net proceeds received by the Company from the IPO were approximately $190.7 million, after deducting underwriting discounts and commissions of $14.6 million, and offering expenses payable by the Company of $3.4 million. No offering expenses were paid directly or indirectly to any of our directors or officers (or their associates) or persons owning 10% or more of any class of our equity securities or to any other affiliates.

There has been no material change in our planned use of the net proceeds from the offering as described in our final prospectus.

Purchases of Equity Securities by the Issuer or Affiliated Purchasers

None.

Item 6. ***Reserved***

Not Applicable.

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

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and related notes appearing elsewhere in this Annual Report on Form 10-K (Annual Report). Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report, 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, our actual results could differ materially from the results described in, or implied by, the forward-looking statements contained in the following discussion and analysis. You should carefully read the "Cautionary Note Regarding Forward Looking Statements" and "Risk Factors" sections of this Annual Report to gain an understanding of the important factors that could cause actual results to differ materially from our forward-looking statements contained in the following discussion and analysis.

Overview

We are a biotechnology company that aims to transform the lives of patients by establishing EEV therapeutics as a new class of medicines and we aim to become the world's foremost intracellular therapeutics company. Through our proprietary, highly versatile and modular EEV platform (EEV Platform), we are building a robust development portfolio of EEV therapeutic candidates designed to enable the efficient intracellular delivery of therapeutics in various organs and tissues with an improved therapeutic index.

Since our inception, we have devoted substantially all our resources to research and development efforts relating to our EEV Platform, advancing development of our portfolio of programs and general and administrative support for these operations, including raising capital. To date, we have financed our operations primarily through the sales of our preferred stock, and most recently, with proceeds from the sale of our common stock in our initial public offering (IPO). In November 2021, we completed our IPO pursuant to which we issued and sold 10,436,250 shares of our common stock, including 1,361,250 shares of common stock pursuant to the full exercise of the underwriters' option to purchase additional shares at a public offering price of $20.00 per share. We received aggregate net proceeds from our IPO of $190.7 million after deducting underwriting discounts and commissions of $14.6 million and offering expenses payable of $3.4 million.

We have incurred losses since our inception. Our net losses were $51.2 million and $26.5 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021, we had an accumulated deficit of $93.7 million. We expect to continue to generate operating losses and negative operating cash flows for the foreseeable future as we advance our platform and EEV therapeutic candidates into later stages of preclinical development and, if successful, clinical development. We will not generate any revenue from product sales unless and until we successfully complete clinical development and obtain regulatory approval for one or more therapeutic candidates, if ever. If we obtain regulatory approval for any therapeutic candidates, we expect to incur significant expenses related to developing our internal commercialization capability to support product sales, marketing and distribution.

Furthermore, we expect to incur additional costs associated with operating as a public company, including significant legal, accounting, investor relations and other expenses that we did not incur as a private company. As a result, we will need substantial additional funding to support our continuing operations and pursue our growth strategy, as we advance therapeutic candidates through preclinical and, if successful, into clinical development, seek regulatory approval, prepare for and, if any therapeutic candidates are approved, proceed to commercialization and operate as a public company. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations through the sale of equity, debt financings or other capital sources, including potential collaborations with other companies or other strategic transactions.

If we are unable to obtain funding, we will be forced to delay, reduce, or eliminate some or all of our research and development programs, product portfolio expansion and ultimate commercialization efforts, which would adversely affect our business prospects, or we may be unable to continue operations. Although we continue to pursue these plans, we may not be successful in obtaining sufficient funding on terms acceptable to us to fund continuing operations, if at all.

Because of the numerous risks and uncertainties associated with product development, we are unable to predict the timing or amount of increased expenses or when or if we will be able to achieve or maintain profitability. Even if we can generate product sales, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

As of December 31, 2021, we had cash and cash equivalents of $291.1 million. We believe that our cash and cash equivalents as of December 31, 2021 will enable us to fund our operating expenses and capital expenditure requirements into the second half of 2024. We have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we expect. See "Management's Discussion and Analysis of Financial Condition and Results of Operations—Liquidity and Capital Resources." To finance our operations beyond that point we will need to raise additional capital, which cannot be assured.

Impact of the Ongoing COVID-19 Pandemic on Our Business

The duration of the ongoing COVID-19 pandemic and the extent to which it may directly or indirectly impact our business, results of operations and financial condition will depend on future developments that are highly uncertain, subject to change and difficult to predict, including the duration of the outbreak, new information that may emerge concerning the severity of COVID-19, such as new strains of the virus, including the Delta and Omicron variants and any future variants that may emerge, which may impact rates of infection and vaccination efforts, developments or perceptions regarding the safety of vaccines and the extent and effectiveness of actions to contain COVID-19 or treat its impact, including vaccination campaigns and lockdown measures, among others. At times during the pandemic, we, our contract manufacturing organizations (CMOs), and our contract research organizations (CROs), experienced temporary reductions in certain operations that have since normalized. We, together with our CMOs and CROs, are closely monitoring the impact of the ongoing COVID-19 pandemic on these operations. Additionally, to provide a safe work environment for our employees, we have implemented various measures including limiting on-site presence to essential employees, providing for social distancing, increased sanitization of our facilities and providing personal protective equipment for our employees. We are continuing to monitor the impact and effects of the ongoing COVID-19 pandemic and our response to it, and we expect to continue to take actions as may be required or recommended by government authorities or as we determine are in the best interests of our employees and other business partners in light of the pandemic.

We have not incurred any significant impairment losses in the carrying values of our assets as a result of the pandemic and we are not aware of any specific related event or circumstance that would require us to revise our estimates reflected in our audited consolidated financial statements included elsewhere in this Annual Report. Our estimates of the impact on our business may change based on new information that may emerge concerning COVID-19 and the actions to contain it or treat its impact and the economic impact on local, regional, national and international markets.

Components of Our Results of Operations

Revenue

To date, we have not generated any revenue. We do not expect to generate any revenue from the sale of products for the foreseeable future. If our development efforts for our therapeutic candidates are successful and result in regulatory approval or we successfully enter into collaboration or license arrangements with third parties, we may generate revenue in the future from product sales, payments from collaboration or license arrangements that we may enter into with third parties, or any combination thereof.

Operating 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 programs. These expenses include:

- personnel-related expenses, including salaries, related benefits, and stock-based compensation expense for individuals engaged in research and development functions;
- expenses incurred in connection with the discovery and preclinical development of our therapeutic candidates and research programs, including under agreements with third parties, such as consultants, contractors, and CROs;
- the cost of developing and validating our manufacturing process for use in our preclinical studies and potential future clinical trials, including the cost of raw materials used in our research and development activities, and engaging with third party CMOs;
- the cost of laboratory supplies and research materials;
- the costs of payments made under third-party licensing agreements and related future payments should certain development and regulatory milestones be achieved; and
- facilities, depreciation and other direct and allocated expenses, including rent and other operating costs, incurred as a result of our research and development activities.

We expense research and development costs as incurred. Non-refundable advance payments that we make for goods or services to be received in the future for use in research and development activities are recorded as prepaid expenses. The prepaid amounts are expensed as the related goods are delivered or the services are performed, or when it is no longer expected that the goods will be delivered or the services rendered. Upfront payments under license agreements are expensed upon receipt of the license and annual maintenance fees under license agreements are expensed in the period in which they are incurred. Milestone payments under license agreements are accrued, with a corresponding expense being recognized, in the period in which the milestone is determined to be probable of achievement and the related amount is reasonably estimable.

As a preclinical-stage company in the early phases of development, our research and development costs are often devoted to proof-of-concept studies and our overall EEV Platform that underpins our therapeutic candidates. Our direct, external research and development expenses consist primarily of fees paid to outside consultants, CROs, CMOs and research laboratories in connection with our process development, manufacturing and clinical development activities. Our direct external research and development expenses also include fees incurred under license and intellectual property purchase agreements. We expect to track these external research and development costs on a program-by-program basis as we identify specific programs and product candidates to advance into clinical development.

We do not allocate employee costs, costs associated with our development efforts and facilities, including depreciation or other indirect costs, to specific programs because these costs are deployed across multiple programs and, as such, are not separately classified. We use internal resources and third-party consultants primarily to conduct our research and development activities as well as for managing our process development, manufacturing and clinical development activities.

Therapeutic 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 that our research and development expenses will increase substantially in connection with our platform development efforts and planned preclinical and clinical development activities in the near term and in the future. We expect that the research and development expenses of our programs will increase in the near term as we initiate investigational new drug (IND)-enabling activities for our therapeutic candidates. Therefore, we cannot reasonably estimate or know the nature, timing, and costs of the efforts that will be necessary to complete the preclinical and clinical development of any of our therapeutic candidates. The successful development of our therapeutic candidates is highly uncertain. This is due to the numerous risks and uncertainties associated with product development, including the following:

- the scope, timing, rate of progress and expenses of our ongoing and potential future research activities, including preclinical and IND-enabling studies, clinical trials and other research and development activities we decide to pursue;
- the successful initiation, enrollment, and completion of clinical trials under current good clinical practices;
- the timing of filing and acceptance of INDs or comparable foreign applications that allow commencement of future clinical trials for our therapeutic candidates;
- whether our therapeutic candidates show safety and efficacy in our clinical trials and an acceptable risk-benefit profile in the intended populations;
- our ability to hire and retain key research and development personnel;
- our ability to successfully develop, obtain regulatory and marketing approvals of our therapeutic candidates for the expected indications and patient populations;
- our ability to establish and maintain agreements with third-party manufacturers for clinical supply for our clinical trials and commercial manufacturing, if our therapeutic candidates are approved;
- commercializing therapeutic candidates, if and when approved, whether alone or in collaboration with others;
- our ability to maintain a continued acceptable safety, tolerability, and efficacy profile of our therapeutic candidates following approval;
- our ability to establish new licensing or collaboration arrangements to support our potential therapeutic candidates on favorable business terms;
- any decisions we make to discontinue, delay or modify our programs to focus on others;
- obtaining, maintaining, protecting and enforcing patent and trade secret protection and regulatory exclusivity for our therapeutic candidates;
- obtaining and maintaining adequate coverage and reimbursement from third party payors; and
- the effects of the ongoing COVID-19 pandemic.

A change in the outcome of any of these variables with respect to the development of any of our therapeutic candidates could significantly change the costs and timing associated with the development of that therapeutic candidate. We may never succeed in obtaining regulatory approval for any of our therapeutic candidates.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and personnel-related costs, including stock-based compensation, for our personnel in executive, legal, finance and accounting, corporate and business development, human resources, and other administrative functions. General and administrative expenses also include: legal fees relating to intellectual property and corporate matters; professional fees paid for accounting, auditing, consulting, and tax services; insurance costs; travel expenses; and facility costs not otherwise included in research and development expenses.

We anticipate that our general and administrative expenses will increase in the future as we increase our headcount to support our continued research activities and development of our programs and EEV Platform. We also anticipate that we will incur increased accounting, audit, legal, regulatory, compliance, director and officer insurance, and investor and public relations expenses associated with operating as a public company.

Other Income (Expense)

Interest Income

Interest income consists of interest earned on our invested cash and cash equivalents balances.

Other Income (Expense), Net

Other income (expense), net consists primarily of gains and losses on disposal of fixed assets and gains and losses on foreign currency transactions.

Income Taxes

Since our inception, we have not recorded any income tax benefits for the net losses we have incurred or for the research and development tax credits earned in each year and interim period as we believe, based upon the weight of available evidence, that it is more likely than not that all our net operating loss carryforwards and tax credit carryforwards will not be realized.

As of December 31, 2021, we had federal net operating loss carryforwards of $93.1 million, which may be available to offset future taxable income, of which $3.2 million expire at various dates beginning in 2036 and the remaining $89.9 million do not expire but are limited in their usage to an annual deduction equal to 80% of annual taxable income. In addition, as of December 31, 2021, we had state net operating loss carryforwards of $88.0 million, which may be available to offset future taxable income and expire at various dates beginning in 2036. As of December 31, 2021, we also had federal and state research and development tax credit carryforwards of $2.3 million and $1.2 million, respectively, which may be available to reduce future tax liabilities and expire at various dates beginning in 2039 and 2034, respectively.

Critical Accounting Policies and Significant Judgments and Estimates

Our management's discussion and analysis of financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with generally accepted accounting principles in the United States. The preparation of our consolidated financial statements and related disclosures requires us to make judgments, estimates and assumptions that affect the reported amounts of assets and liabilities, costs and expenses and the disclosure of contingent assets and liabilities in our consolidated financial statements. We base our estimates on historical experience, known trends and events and various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. We evaluate our estimates and assumptions on an ongoing basis. Our actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in Note 2 to our consolidated financial statements appearing elsewhere in this Annual Report, we believe that the following accounting policies are those most critical to the judgments and estimates used in the preparation of our consolidated financial statements.

Accrued Research and Development Expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development expenses. This process involves estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of actual costs. We make estimates of our accrued expenses as of each balance sheet date in the consolidated financial statements based on facts and circumstances known to us at that time. We periodically corroborate the accuracy of these estimates with the service providers and make adjustments, if necessary. Examples of estimated accrued research and development expenses include those related to fees paid to:

- vendors in connection with discovery and preclinical development activities;
- CROs in connection with preclinical studies and testing; and

- third-party manufacturers in connection with the development and scale up activities and the production of materials.

We base the expense recorded related to contract research and manufacturing on our estimates of the services received and efforts expended pursuant to quotes and contracts with multiple service providers that conduct services and supply materials. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. In accruing service fees, we estimate the time period over which services were performed and the level of effort expended in each period. If the actual timing of the performance of services or the level of effort varies from the estimate, we adjust the accrual accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in reporting amounts that are too high or too low in any particular period. While the majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met, some require advance payments. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the expense. We record these as prepaid expenses on our consolidated balance sheets.

Stock-Based Compensation

We account for all stock-based compensation awards granted as stock-based compensation expense at fair value in accordance with FASB ASC Topic 718, *Compensation—Stock Compensation* (ASC 718). Our stock-based payments include stock options and grants of common stock restricted for vesting conditions. The measurement date for awards is the date of grant, and stock-based compensation costs are recognized as expense over the requisite service period, which is generally the vesting period, on a straight-line basis. Stock-based compensation expense is classified in the accompanying consolidated statements of operations based on the function to which the related services are provided. Forfeitures are recorded as they occur.

The fair value of each stock option grant is estimated on the date of grant using the Black-Scholes option-pricing model, which requires inputs based on certain subjective assumptions, including the expected share price volatility, the expected term of the option, the risk-free interest rate for a period that approximates the expected term of the option, and our expected dividend yield. Prior to our IPO, there was no public market for our common stock, and consequently, the estimated fair value of our common stock was determined by our board of directors as of the date of each option grant, with input from management, considering third-party valuations of our common stock as well as our board of directors' assessment of additional objective and subjective factors that it believed were relevant and which may have changed from the date of the most recent third-party valuation through the date of the grant. These third-party valuations were performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants' Accounting and Valuation Guide, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation* (Practice Aid). The Practice Aid identifies various available methods for allocating the enterprise value across classes of series of capital stock in determining the fair value of our common stock at each valuation date. Since our IPO, we have determined the fair market value of our common stock using the closing price of our common stock as reported on the Nasdaq Global Market.

Subsequent to the IPO, the fair value of the common stock underlying our stock-based awards is the closing price of our common stock on the date of grant.

Recently Issued Accounting Pronouncements

See Note 2, *Summary of Significant Accounting Policies*, in the notes to our consolidated financial statements for a description of recent accounting pronouncements applicable to our business.

Results of Operations

Comparison of the years ended December 31, 2021 and 2020

(in thousands)	Year Ended December 31, 2021	2020	Change
Operating expenses:			
Research and development	$ 35,926	$ 21,102	$ 14,824
General and administrative	15,201	5,565	9,636
Total operating expenses	51,127	26,667	24,460
Loss from operations	(51,127)	(26,667)	(24,460)
Other income (expense):			
Interest and other income (expense), net	(31)	144	(175)
Total other income (expense), net	(31)	144	(175)
Net loss	$ (51,158)	$ (26,523)	$ (24,635)

Research and Development Expenses

(in thousands)	Year Ended December 31, 2021	2020	Change
External fees for outside research and consulting services (including third-party CROs)	$ 10,973	$ 8,713	$ 2,260
Personnel related (including stock-based compensation)	13,187	6,106	7,081
Lab supplies used in research and development activities	4,873	3,470	1,403
Facility and equipment related costs (including depreciation) and other unallocated costs	6,893	2,813	4,080
Total research and development expenses	$ 35,926	$ 21,102	$ 14,824

Research and development expenses were $35.9 million for the year ended December 31, 2021, compared to $21.1 million for the year ended December 31, 2020. The increase of $14.8 million in research and development expenses was primarily attributable to:

- an increase of $7.1 million in personnel-related costs driven by increased headcount in our research and development function, inclusive of stock-based compensation expense of $0.9 million and $0.1 million for the years ended December 31, 2021 and 2020, respectively;
- an increase of $4.1 million in facility and equipment-related costs, including depreciation, and other allocated miscellaneous expenses in connection with the operating lease for our corporate headquarters;
- an increase of $2.2 million in external expenses associated with discovery and preclinical studies performed by outside consulting services, including third party CROs; and
- an increase of $1.4 million in lab supplies due to the increased investment in research and development activities.

We expect our research and development expenses will continue to increase as we continue our current research and development activities, initiate new research programs, continue our preclinical development of therapeutic candidates and progress ENTR-601-44, and future product candidates, into clinical trials.

General and Administrative Expenses

General and administrative expenses for the year ended December 31, 2021 were $15.2 million, compared to $5.6 million for the year ended December 31, 2020. The increase of $9.6 million was primarily attributable to the following:

- a $5.2 million increase in personnel-related costs, primarily as a result of the increase in headcount in our general and administrative function, inclusive of stock-based compensation expense of $1.6 million and $0.2 million for the years ended December 31, 2021 and 2020, respectively;

- a $2.1 million increase in professional services costs, primarily attributable to legal and outside consulting services to support our continued research activities and development of our programs;

- a $1.3 million increase in other miscellaneous expenses, including fees attributable to operating as a public company; and

- a $1.0 million increase in facility and equipment-related expenses in connection with the operating lease for our corporate headquarters.

Other Income (Expense)

Total other expense was less than $0.1 million for the year ended December 31, 2021, compared to total other income of $0.1 million for the year ended December 31, 2020. Total other income included interest income on our cash equivalents, which are primarily invested in money market funds which decreased less than $0.1 million from December 31, 2020 to December 31, 2021.

Liquidity and Capital Resources

Sources of Liquidity

Since our inception in 2016, we have incurred significant operating losses. Our net losses were $51.2 million and $26.5 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021 and December 31, 2020, we had an accumulated deficit of $93.7 million and $42.5 million, respectively. We expect to incur significant expenses and operating losses for the foreseeable future as we further our platform development and advance the preclinical and, if successful, the clinical development of our programs. To date, we have funded our operations primarily with $201.8 million in proceeds from the sale of preferred stock, and most recently, with proceeds from the sale of common stock in our IPO completed in November 2021, including the underwriters' exercise of their over-allotment option to purchase additional shares of common stock. As of December 31, 2021, we had cash and cash equivalents of $291.1 million.

Cash Flows

The following table summarizes our cash flows for each of the periods presented:

	Year Ended December 31,	
(in thousands)	**2021**	**2020**
Net cash used in operating activities	$ (50,862)	$ (25,570)
Net cash used in investing activities	(4,580)	(2,318)
Net cash provided by financing activities	307,461	50,089
Net increase in cash and cash equivalents	$ 252,019	$ 22,201

Operating Activities

For the year ended December 31, 2021, net cash used in operating activities was $50.9 million, consisting primarily of our net loss of $51.2 million, partially offset by stock-based compensation expense of $2.5 million, depreciation expense of $1.1 million, loss on disposal of assets of $0.1 million, and net cash used in our operating assets and liabilities of $3.4 million.

For the year ended December 31, 2020, net cash used in operating activities was $25.6 million, consisting primarily of our net loss of $26.5 million, partially offset by stock-based compensation expense of $0.3 million, depreciation expense of $0.3 million, and net cash provided by changes in our operating assets and liabilities of $0.3 million.

Investing Activities

Net cash used in investing activities was $4.6 million and $2.3 million for the years ended December 31, 2021 and 2020, respectively, and resulted from our purchases of property and equipment.

Financing Activities

Net cash provided by financing activities was $307.5 million for the year ended December 31, 2021, consisting of $115.8 million of net proceeds from the sale of our Series B Preferred Stock in March 2021 and $190.7 million of aggregate net proceeds from our IPO in November 2021, and stock option exercises, inclusive of early exercises of stock options, of $1.0 million.

Net cash provided by financing activities was $50.1 million for the year ended December 31, 2020, consisting of $49.8 million of net proceeds from the sale of our Series A Preferred Stock in January 2020 and August 2020, and stock option exercises, inclusive of early exercises of stock options, of $0.3 million.

Funding Requirements

We expect to incur significant expenses and operating losses for the foreseeable future as we advance the preclinical and, if successful, the clinical development of our programs. In addition, we expect to incur additional costs associated with operating as a public company. Our operating expenses and future funding requirements are expected to increase substantially as we continue to advance our portfolio of programs. We believe that our cash and cash equivalents as of December 31, 2021 will enable us to fund our operating expenses and capital expenditure requirements into the second half of 2024. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we expect.

Because of the numerous risks and uncertainties associated with research, development, and commercialization of our candidates, we are unable to estimate the exact amount of our working capital requirements. Our future capital requirements will depend on many factors, including costs associated with:

- the continuation of our current research programs and our preclinical development of therapeutic candidates from our current research programs;
- seeking to identify additional research programs and additional therapeutic candidates;
- advancing our existing and future therapeutic candidates into clinical development;
- initiating preclinical studies and clinical trials for any therapeutic candidates we identify and develop or expand development of existing programs into additional indications;
- maintaining, expanding, enforcing, defending and protecting our intellectual property portfolio and providing reimbursement of third-party expenses related to our patent portfolio;
- timing of manufacturing for our therapeutic candidates and commercial manufacturing if any therapeutic candidate is approved;
- establishing and maintaining clinical and commercial supply for the development and manufacture of our therapeutic candidates;
- seeking regulatory and marketing approvals for any of our therapeutic candidates that we develop, if any;
- seeking to identify, establish and maintain additional collaborations and license agreements, and the success of those collaborations and license agreements;
- ultimately establishing a sales, marketing, and distribution infrastructure to commercialize any platforms for which we may obtain marketing approval, either by ourselves or in collaboration with others;

- generating revenue from commercial sales of therapeutic candidates we may develop for which we receive marketing approval;
- hiring additional personnel including research and development, clinical, and commercial personnel;
- adding operational, financial, and management information systems and personnel, including personnel to support our product development;
- achieve sufficient market acceptance, coverage and adequate reimbursement from third-party payors and adequate market share and revenue for any approved products;
- acquiring or in-licensing products, intellectual property, and technologies; and
- the ongoing costs of operating as a public company.

Until such time, if ever, as we can generate substantial product revenue to support our cost structure, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, and other similar arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our stockholders could be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing and 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. If we raise funds through collaborations or other similar arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or therapeutic candidates or grant licenses on terms that may not be favorable to us and/or may reduce the value of our common stock. If we are unable to raise additional funds when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market our therapeutic candidates even if we would otherwise prefer to develop and market such therapeutic candidates ourselves.

Contractual Obligations and Commitments

The following table summarizes our contractual obligations as of December 31, 2021:

	Payments Due by Period				
(in thousands)	**Total**	**Less Than 1 Year**	**1 to 3 Years**	**4 to 5 Years**	**More Than 5 Years**
Operating lease obligations (1)	$ 16,910	$ 8,526	$ 8,384	$ —	$ —
Total	$ 16,910	$ 8,526	$ 8,384	$ —	$ —

(1) We have the option to terminate our Boston, Massachusetts office and lab space lease after November 30, 2023 upon proper notice without penalty.

We enter into contracts in the normal course of business with CROs, third-party manufacturers, and other third parties for preclinical research studies and testing and manufacturing services. These contracts do not contain minimum purchase commitments and are cancelable by us upon prior written notice. Payments due upon cancellation consist only of payments for services provided or expenses incurred, including noncancelable obligations of our service providers, up to the date of cancellation. These payments are not included in the preceding table as the amount and timing of such payments are not known.

We have also entered into license agreements under which we are obligated to make certain payments. The table above does not include potential success payments, sublicense fees, royalty fees, licensing maintenance fees and reimbursement of patent maintenance costs that we may be required to pay under license agreements. For additional information about our license agreement and amounts that could become payable in the future under such agreements, see “Business—Intellectual property— License agreement with The Ohio State University” and Note 9 Commitments and Contingencies to our consolidated financial statements.

Emerging Growth Company and Smaller Reporting Company Status

We are an "emerging growth company," or EGC, under the Jumpstart Our Business Startups Act of 2012 (the JOBS Act). Section 107 of the JOBS Act provides that an EGC can take advantage of the extended transition period provided in Section 7(a)(2)(B) of the Securities Act of 1933, as amended, for complying with new or revised accounting standards. Thus, an EGC can delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have elected to avail ourselves of delayed adoption of new or revised accounting standards and, therefore, we will be subject to the same requirements to adopt new or revised accounting standards as private entities.

As an EGC, we may, and intend to, take advantage of certain exemptions and reduced reporting requirements under the JOBS Act. Subject to certain conditions, as an EGC:

- we may present only two years of audited financial statements and only two years of related Management's Discussion and Analysis of Financial Condition and Results of Operations;
- we may avail ourselves of the exemption from providing an auditor's attestation report on our system of internal controls over financial reporting pursuant to Section 404(b) of the Sarbanes-Oxley Act of 2002, as amended (the Sarbanes-Oxley Act);
- we may avail ourselves of the exemption from complying with any requirement that may be adopted by the Public Company Accounting Oversight Board (PCAOB) regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements, known as the auditor discussion and analysis;
- we may provide reduced disclosure about our executive compensation arrangements; and
- we may not require nonbinding advisory votes on executive compensation or stockholder approval of any golden parachute payments.

We will remain an EGC until the earliest to occur of (i) the last day of the fiscal year following the fifth anniversary of the completion of our IPO, (ii) the last day of the fiscal year in which we have total annual gross revenues of $1.07 billion or more, (iii) the date on which we have issued more than $1.0 billion in non-convertible debt during the previous rolling three-year period or (iv) the date on which we are deemed to be a large accelerated filer under the Securities Exchange Act of 1934, as amended (the Exchange Act).

We are also a "smaller reporting company," meaning that the market value of our stock held by non-affiliates is less than $700 million and our annual revenue was less than $100 million during the most recently completed fiscal year. We may continue to be a smaller reporting company if either (i) the market value of our stock held by non-affiliates is less than $250 million or (ii) our annual revenue was less than $100 million during the most recently completed fiscal year and the market value of our stock held by non-affiliates is less than $700 million. If we are a smaller reporting company at the time we cease to be an emerging growth company, we may continue to rely on exemptions from certain disclosure requirements that are available to smaller reporting companies. Specifically, as a smaller reporting company we may choose to present only the two most recent fiscal years of audited financial statements in our Annual Report on Form 10-K and, similar to emerging growth companies, smaller reporting companies have reduced disclosure obligations regarding executive compensation.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk

We are a smaller reporting company as defined by Rule 12b-2 of the Exchange Act and are not required to provide the information required under this item.

Item 8. Financial Statements and Supplementary Data

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Entrada Therapeutics, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Entrada Therapeutics, Inc. (the Company) as of December 31, 2021 and 2020, the related consolidated statements of operations, redeemable convertible preferred stock and stockholders' (deficit) equity and cash flows for the years then ended, and the related notes (collectively referred to as the “consolidated financial statements”). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2021 and 2020, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2021, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

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

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

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

/s/ Ernst & Young LLP

We have served as the Company’s auditor since 2021.
Boston, Massachusetts
March 15, 2022

ENTRADA THERAPEUTICS, INC.

CONSOLIDATED BALANCE SHEETS

(In thousands, except share and per share amounts)

	December 31, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 291,064	$ 39,045
Prepaid expenses and other current assets	7,636	904
Total current assets	298,700	39,949
Property and equipment, net	6,261	3,037
Other non-current assets	872	541
Total assets	$ 305,833	$ 43,527
Liabilities, Redeemable Convertible Preferred Stock and Stockholders' (Deficit) Equity		
Current liabilities:		
Accounts payable	$ 706	$ 1,602
Accrued expenses and other current liabilities	6,013	1,757
Total current liabilities	6,719	3,359
Deferred rent, net of current portion	396	—
Total liabilities	7,115	3,359
Commitments and contingencies (Note 9)		
Redeemable convertible preferred stock, par value $0.0001 (Note 6)	—	81,658
Stockholders' (deficit) equity:		
Common stock, par value $0.0001; 150,000,000 and 113,259,306 shares authorized as of December 31, 2021 and December 31, 2020, respectively; 31,336,092 and 1,283,545 shares issued as of December 31, 2021 and December 31, 2020, respectively; 31,224,336 and 1,244,139 shares outstanding as of December 31, 2021 and December 31, 2020, respectively	3	—
Additional paid-in capital	392,384	1,021
Accumulated deficit	(93,669)	(42,511)
Total stockholders' (deficit) equity	298,718	(41,490)
Total liabilities, redeemable convertible preferred stock and stockholders' (deficit) equity	$ 305,833	$ 43,527

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

ENTRADA THERAPEUTICS, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS

(In thousands, except share and per share amounts)

	Year Ended December 31, 2021	2020
Operating expenses:		
Research and development	$ 35,926	$ 21,102
General and administrative	15,201	5,565
Total operating expenses	51,127	26,667
Loss from operations	(51,127)	(26,667)
Other (expense) income:		
Interest and other (expense) income, net	(31)	144
Total other (expense) income, net	(31)	144
Net loss	$ (51,158)	$ (26,523)
Net loss per share attributable to common stockholders, basic and diluted	$ (8.16)	$ (24.00)
Weighted-average common shares outstanding, basic and diluted	6,267,776	1,105,260

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

ENTRADA THERAPEUTICS, INC.

CONSOLIDATED STATEMENTS OF REDEEMABLE CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' (DEFICIT) EQUITY

(In thousands, except share amounts)

	Redeemable Convertible Preferred Stock		Common Stock		Additional Paid-in Capital	Accumulated Deficit	Total Stockholders' (Deficit) Equity
	Shares	Amount	Shares	Amount			
Balances at December 31, 2019	37,269,149	$ 31,816	1,004,310	$ —	$ 470	$ (15,988)	$ (15,518)
Issuance of Series A redeemable convertible preferred stock, net of issuance costs of $158	48,030,736	49,842	—	—	—	—	—
Issuance of common stock upon exercise of stock options	—	—	129,607	—	214	—	214
Vesting of restricted common stock	—	—	95,770	—	1	—	1
Vesting of early exercised options	—	—	14,452	—	11	—	11
Stock-based compensation	—	—	—	—	325	—	325
Net loss	—	—	—	—	—	(26,523)	(26,523)
Balances at December 31, 2020	85,299,885	$ 81,658	1,244,139	$ —	$ 1,021	$ (42,511)	$ (41,490)
Issuance of Series B redeemable convertible preferred stock, net of issuance costs of $420	53,522,099	115,831	—	—	—	—	—
Conversion of redeemable convertible preferred stock upon initial public offering	(138,821,984)	(197,489)	19,185,183	2	197,487	—	197,489
Issuance of common stock from initial public offering, net of issuance costs of $18,034	—	—	10,436,250	1	190,690	—	190,691
Issuance of common stock upon exercise of stock options	—	—	223,838	—	410	—	410
Vesting of restricted common stock	—	—	11,537	—	—	—	—
Vesting of early exercised options	—	—	123,389	—	250	—	250
Stock-based compensation	—	—	—	—	2,526	—	2,526
Net loss	—	—	—	—	—	(51,158)	(51,158)
Balances at December 31, 2021	—	$ —	31,224,336	$ 3	$ 392,384	$ (93,669)	$ 298,718

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

ENTRADA THERAPEUTICS, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS

(In thousands)

	Year Ended December 31, 2021	2020
Cash flows from operating activities:		
Net loss	$ (51,158)	$ (26,523)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation expense	1,117	326
Loss on disposal of property and equipment	74	20
Stock-based compensation expense	2,526	325
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	(6,733)	(311)
Other non-current assets	(331)	(541)
Accounts payable	(715)	631
Accrued expenses and other current liabilities	3,962	578
Deferred rent	396	(75)
Net cash used in operating activities	(50,862)	(25,570)
Cash flows from investing activities:		
Purchases of property and equipment	(4,580)	(2,318)
Net cash used in investing activities	(4,580)	(2,318)
Cash flows from financing activities:		
Proceeds from issuance of redeemable convertible preferred stock, net of issuance costs	115,831	49,842
Proceeds from issuance of common stock upon initial public offering, net of issuance costs	190,691	—
Proceeds from exercise of stock options	410	213
Proceeds from the early exercise of stock options	529	34
Net cash provided by financing activities	307,461	50,089
Net increase in cash and cash equivalents	252,019	22,201
Cash and cash equivalents at beginning of year	39,045	16,844
Cash and cash equivalents at end of year	$ 291,064	$ 39,045
Supplemental cash flow disclosures:		
Purchases of property and equipment included in accounts payable and accrued expenses	$ 155	$ 320
Conversion of preferred stock to common stock upon initial public offering	$ 197,489	$ —
Vesting of restricted stock subject to repurchase	$ —	$ 1
Vesting of options early exercised subject to repurchase	$ 250	$ 11

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

ENTRADA THERAPEUTICS, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

For the Years Ended December 31, 2021 and 2020

1. Nature of the Business

Organization

Entrada Therapeutics, Inc. (Entrada or the Company) aims to transform the lives of patients by establishing Endosomal Escape Vehicle (EEV™) therapeutics as a new class of medicines and aim to become the world's foremost intracellular therapeutics company. The Company was incorporated in Delaware on September 22, 2016 and its principal offices are located in Boston, Massachusetts.

Initial Public Offering

In November 2021, the Company completed its initial public offering (IPO) in which the Company issued and sold 10,436,250 shares of its common stock, including 1,361,250 shares pursuant to the full exercise of the underwriters' option to purchase additional shares, at a public offering price of $20.00 per share, for aggregate gross proceeds of $208.7 million. The Company received $190.7 million in net proceeds, after deducting underwriting discounts and offering expenses payable. In connection with the IPO, all outstanding shares of the Company's redeemable convertible preferred stock converted into 19,185,183 shares of the Company's common stock.

On October 22, 2021, in connection with the Company's IPO, the Company effected a 1-for-7.235890014 reverse stock split of the Company's common stock. All common shares, stock options, and per share information presented in the accompanying consolidated financial statements and notes thereto have been adjusted, where applicable, to reflect the reverse stock split on a retroactive basis for all periods presented, including reclassification of par and additional paid-in capital amounts. The per share par value and authorized number of shares of the Company's common stock were not adjusted as a result of the reverse stock split.

Liquidity and Capital Resources

Since its inception, the Company has devoted substantially all of its resources to its research and development efforts relating to its proprietary, highly versatile and modular EEV platform (EEV Platform), advancing development of its portfolio of programs and general and administrative support for these operations, including raising capital. The Company is subject to risks and uncertainties common to early-stage companies in the biotechnology industry, including, but not limited to, technical risks associated with the successful research, development and manufacturing of therapeutic candidates, development by competitors of new technological innovations, dependence on key personnel, protection of proprietary technology, compliance with government regulations, and the ability to secure additional capital to fund operations. Therapeutic candidates currently under development will require significant additional research and development efforts, including extensive preclinical and clinical testing and regulatory approval prior to commercialization. These efforts will require significant amounts of additional capital, adequate personnel and infrastructure. Even if the Company's product development efforts are successful, it is uncertain when, if ever, the Company will realize revenue from product sales.

In accordance with Accounting Standards Codification (ASC) 205-40, *Going Concern*, the Company evaluated whether there are conditions and events, considered in the aggregate, that raise substantial doubt about its ability to continue as a going concern within one year after the date that the consolidated financial statements are issued. The Company has incurred losses since its inception, including losses of $51.2 million and $26.5 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021, the Company had an accumulated deficit of $93.7 million. To date, the Company has funded its operations primarily through the sale of equity securities. The Company expects to continue to generate operating losses and negative operating cash flows for the foreseeable future.

The Company expects that its cash and cash equivalents of $291.1 million as of December 31, 2021 will be sufficient to fund its operations and capital expenditure requirements for at least the next twelve months from the date of issuance of these consolidated financial statements. The Company will need additional financing to support its continuing operations and pursue its business strategy and may pursue additional cash resources through a combination of equity offerings, debt financings, collaborations, strategic alliances, licensing, or other arrangements. The Company

may be unable to raise additional funds or enter into such other agreements when needed or on favorable 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 its ability to pursue its business strategy. The Company will need to generate significant revenue to achieve profitability, and it may never do so.

2. Summary of Significant Accounting Policies

Basis of Presentation

The accompanying consolidated financial statements reflect the operations of the Company and have been prepared in conformity with generally accepted accounting principles in the United States of America (GAAP). Any reference in these notes to applicable guidance is meant to refer to the authoritative GAAP as found in the ASC and Accounting Standards Update (ASU) of the Financial Accounting Standards Board (FASB).

Principles of Consolidation

The accompanying consolidated financial statements include those of the Company and its wholly-owned subsidiary. All intercompany balances and transactions have been eliminated in consolidation.

Use of Estimates

The preparation of the Company's consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets, liabilities and expenses, 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, but are not limited to accrual and prepayment of research and development expenses and stock-based compensation. The Company bases its estimates on historical experience, known trends, and other market-specific or other relevant factors that it believes to be reasonable under the circumstances. On an ongoing basis, management evaluates its estimates, as there are changes in circumstances, facts, and experience. Changes in estimates are recorded in the period in which they become known. Actual results may differ from those estimates or assumptions.

Segment Information

The Company manages its operations as a single segment. The Company's chief operating decision maker, its Chief Executive Officer, manages the Company's operations on a consolidated basis for the purposes of assessing performance and making operating decisions. All of the Company's long-lived assets are located in the United States.

Cash and Cash Equivalents

Cash and cash equivalents consist of standard checking accounts and money market account funds that invest primarily in U.S. government-backed securities and treasuries. The Company considers all highly liquid investments with an original maturity of three months or less at the date of purchase to be cash equivalents. Cash equivalents are stated at cost, which is substantially equivalent to fair value. As of December 31, 2021 and 2020, the Company has no restricted cash.

Concentrations of Credit Risk and Off-Balance Sheet Risk

Financial instruments that potentially subject the Company to significant concentration of credit risk consist primarily of cash and cash equivalents. Periodically, the Company may maintain deposits in financial institutions in excess of government insured limits. Management believes that the Company is not exposed to significant credit risk as the Company's deposits are held at financial institutions that management believes to be of high credit quality, and the Company has not experienced any losses on these deposits.

Fair Value Measurements

ASC Topic 820, *Fair Value Measurement* (ASC 820), establishes a fair value hierarchy for instruments measured at fair value that distinguishes between assumptions based on market data (observable inputs) and the

Company's own assumptions (unobservable inputs). Observable inputs are inputs that market participants would use in pricing the asset or liability based on market data obtained from sources independent of the Company. Unobservable inputs are inputs that reflect the Company's assumptions about the inputs that market participants would use in pricing the assets or liability and are developed based on the best information available under the circumstances. ASC 820 identifies fair value as the price that would be received to sell an asset or paid to transfer a liability, in an orderly transaction between market participants at the measurement date.

As a basis for considering market participant assumptions in fair value measurements, ASC 820 establishes a three-tiered value hierarchy that distinguishes between the following:

- Level 1—Quoted prices in active markets for identical assets or liabilities.
- Level 2—Observable inputs (other than Level 1 quoted prices), such as quoted prices in active markets for similar assets or liabilities, quoted prices in markets that are not active for identical or similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data.
- Level 3—Unobservable inputs that are supported by little or no market activity and that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies, and similar techniques.

To the extent the valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair values requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized as Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

There have been no changes to the valuation methods utilized by the Company during the years ended December 31, 2021 and 2020. The Company evaluates transfers between levels at the end of each reporting period. There were no transfers of financial instruments between levels during the years ended December 31, 2021 and 2020. The carrying amounts of accounts payable and accrued expenses approximate their fair values due to their short-term nature.

Property and Equipment

Property and equipment are stated at cost less accumulated depreciation. Depreciation expense is recognized using the straight line method over the estimated useful life of each asset as follows:

	Estimated Useful Life
Laboratory equipment	5 years
Computer equipment	3 years
Furniture and fixtures	5 years
Leasehold improvements	Lesser of estimated useful life or remaining lease term

Costs for capital assets not yet placed into service are capitalized as construction-in-progress and depreciated once placed into service. Upon retirement or sale, the cost of assets disposed of and the related accumulated depreciation are removed from the accounts and any resulting gain or loss is included in other (expense) income. Expenditures for repairs and maintenance that do not improve or extend the life of the respective assets are expensed in operations as incurred.

Impairment of Long-Lived Assets

The Company evaluates its long-lived assets, which consist primarily of property and equipment, for impairment whenever events or changes in circumstances indicate that the carrying amount of such assets may not be recoverable. Recoverability of assets to be held and used is measured by a comparison of the carrying amount of an asset to the future undiscounted net cash flows expected to be generated by the asset. If such assets are considered to be impaired, the impairment to be recognized is measured by the amount by which the carrying amount of the asset exceeds the fair value of the asset. There were no impairment losses recognized during the years ended December 31, 2021 and 2020.

Redeemable Convertible Preferred Stock

The Company recorded redeemable convertible preferred stock at fair value upon issuance, net of any issuance costs. The Company classified stock that was redeemable in circumstances outside of the Company's control outside of permanent equity. No accretion was recognized as the contingent events that could give rise to redemption were not deemed probable.

Deferred Offering Costs

The Company capitalizes incremental legal, professional accounting and other third-party fees that are incurred in the course of preparing for a financing as other non-current assets until the offering is consummated. At the time of the completion of the offering, the costs are reclassified as a reduction of the proceeds of the financing as part of additional paid-in-capital. Should the offering be terminated, deferred offering costs are charged to operations during the period in which the offering is terminated.

Contingencies

The Company records liabilities for legal and other contingencies when information available to the Company indicates that it is probable that a liability has been incurred and the amount of loss can be reasonably estimated. Legal costs in connection with legal and other contingencies are expensed as costs are incurred. No liabilities for legal and other contingencies were accrued as of December 31, 2021 and 2020.

Indemnification Agreements

In the ordinary course of business, the Company may provide indemnification of varying scope and terms to vendors, lessors, contract research organizations (CROs), business partners and other parties with respect to certain matters including, but not limited to, losses arising out of breach of such agreements or from intellectual property infringement claims made by third parties. In addition, the Company has entered into indemnification agreements with members of its board of directors and its executive officers that will require the Company, among other things, to indemnify them against certain liabilities that may arise by reason of their status or service as directors or officers. The maximum potential amount of future payments the Company could be required to make under these indemnification agreements is, in many cases, unlimited. The Company has not incurred any material costs as a result of such indemnifications and is not currently aware of any indemnification claims.

Rent Expense

The Company's real estate operating lease provides for scheduled annual rent increases throughout the lease term. In accordance with ASC Topic 840, *Leases* (ASC 840), the Company recognizes the effects of the scheduled rent increases on a straight-line basis over the full term of the lease. Tenant improvement allowances, if any, provided by the landlord are recorded as deferred rent and amortized as a reduction to rent expense over the lease term.

Research and Development Costs

Research and development costs are charged to expense as incurred. Research and development costs consist of direct and allocated costs incurred in performing research and development activities, including salaries and bonuses, stock-based compensation, employee benefits, facilities costs, third-party license fees related to technology with no alternative future use, laboratory supplies, depreciation, manufacturing expenses, preclinical expenses, consulting and other contracted services. Costs for certain research and development activities are recognized based on the terms of the individual arrangements, which may differ from the pattern of costs incurred, and are reflected in the consolidated financial statements as prepaid or accrued research and development.

Patent Costs

All patent-related costs incurred in connection with filing and prosecuting patent applications are expensed as incurred due to the uncertainty about the recovery of the expenditure. Amounts incurred are classified as general and administrative expenses.

Stock-Based Compensation

The Company's stock-based compensation program allows for grants of stock options and restricted stock awards. Grants are awarded to employees and non-employees, including the Company's board of directors.

The Company accounts for its stock-based compensation in accordance with ASC Topic 718, *Compensation-Stock Compensation* (ASC 718). ASC 718 requires all stock-based payments to employees, non-employees and directors, to be recognized as expense in the consolidated statements of operations based on their grant date fair values. The Company estimates the fair value of options granted using the Black-Scholes option pricing model (Black-Scholes) for stock option grants to both employees and non-employees. The fair value of the Company's common stock is used to determine the fair value of restricted stock awards.

The Company's stock-based compensation awards are subject to service-based vesting conditions. Compensation expense related to awards to employees, directors and non-employees with service-based vesting conditions is recognized on a straight-line basis based on the grant date fair value over the associated service period of the award, which is generally the vesting term.

Black-Scholes requires inputs based on certain subjective assumptions, including (i) the expected stock price volatility, (ii) the expected term of the award, (iii) the risk-free interest rate and (iv) expected dividends. The Company determines the expected volatility using a blended approach encompassing its historical experience and the historical volatility of a peer group of comparable publicly traded companies with product candidates in similar stages of development to the Company's product candidates. The Company uses the simplified method as prescribed by the SEC Staff Accounting Bulletin No. 107, Share-Based Payment, to calculate the expected term for options granted to employees and non-employees whereby, the expected term equals the arithmetic average of the vesting term and the original contractual term of the options due to its lack of sufficient historical data. The risk-free interest rate is based on U.S. Treasury securities with a maturity date commensurate with the expected term of the associated award. The expected dividend yield is assumed to be zero as the Company has never paid dividends and has no current plans to pay any dividends on its common stock. The Company recognizes forfeitures as they occur.

Prior to the Company's IPO, there was no public market for its common stock, and consequently, the estimated fair value of its common stock was determined by the board of directors as of the date of each option grant, with input from management, considering third-party valuations of its common stock as well as its board of directors' assessment of additional objective and subjective factors that it believed were relevant and which may have changed from the date of the most recent third-party valuation through the date of the grant. These third-party valuations were performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants' Accounting and Valuation Guide, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation* (Practice Aid). The Practice Aid identifies various available methods for allocating the enterprise value across classes of series of capital stock in determining the fair value of the Company's common stock at each valuation date.

Subsequent to the Company's IPO, the fair value of the common stock underlying the stock-based awards is the closing price of the Company's common stock on the date of grant.

Restricted common stock awards are subject to service based vesting and repurchase rights. Accordingly, the Company has recorded the proceeds from the issuance of restricted stock as a liability in the consolidated balance sheets. This restricted stock liability is reclassified into stockholders' (deficit) equity as the restricted stock vests.

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

Income Taxes

Income taxes are recorded in accordance with FASB ASC Topic 740, *Income Taxes* (ASC 740), which provides for deferred taxes using an asset and liability approach. The Company accounts for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the consolidated financial statements or in the Company's tax returns. Deferred tax assets and liabilities are determined on the basis of the differences between the consolidated

financial statements and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Changes in deferred tax assets and liabilities are recorded in the provision for income taxes. The Company assesses the likelihood that its deferred tax assets will be recovered from future taxable income and, to the extent it believes, based upon the weight of available evidence, that it is more likely than not that all or a portion of the deferred tax assets will not be realized, a valuation allowance is established through a charge to income tax expense. Potential for recovery of deferred tax assets is evaluated by estimating the future taxable profits expected and considering prudent and feasible tax planning strategies.

The Company accounts for uncertainty in income taxes recognized in the consolidated financial statements by first evaluating the tax position to determine the likelihood that it will be sustained upon external examination by the taxing 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 consolidated financial statements. 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 accounts for interest and penalties related to uncertain tax positions as part of its provision for income taxes.

Net Loss per Share

The Company follows the two-class method when computing net loss per share, as the Company has issued shares that meet the definition of participating securities. The two-class method determines net loss per share for each class of common and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income available to common stockholders for the period to be allocated between common and participating securities based upon their respective rights to receive dividends as if all income for the period had been distributed. During periods of loss, there is no allocation required under the two-class method since the participating securities do not have a contractual obligation to fund the losses of the Company.

Basic net loss per share attributable to common stockholders is computed by dividing the net loss attributable to common stockholders by the weighted average number of common shares outstanding for the period. Diluted net loss attributable to common stockholders is computed by adjusting net loss attributable to common stockholders to reallocate undistributed earnings based on the potential impact of dilutive securities. Diluted net loss per share attributable to common stockholders is computed by dividing the diluted net loss attributable to common stockholders by the weighted average number of common shares outstanding for the period, including potential dilutive common shares assuming the dilutive effect of common stock equivalents. Given that the Company recorded a net loss for each of the periods presented, there is no difference between basic and diluted net loss per share since the effect of common stock equivalents would be antidilutive and are, therefore, excluded from the diluted net loss per share calculation.

Emerging Growth Company Status

The Company qualifies as an “emerging growth company” (EGC), as defined in the Jumpstart Our Business Startups Act (JOBS Act) and may take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not EGCs. The Company may take advantage of these exemptions until it is no longer an EGC under Section 107 of the JOBS Act, which provides that an EGC can take advantage of the extended transition period afforded by the JOBS Act for the implementation of new or revised accounting standards. The Company has elected to avail itself of the extended transition period and, therefore, while the Company is an EGC it will not be subject to new or revised accounting standards the same time that they become applicable to other public companies that are not EGCs, unless it chooses to early adopt a new or revised accounting standard. As a result of this election, the consolidated financial statements may not be comparable to companies that comply with public company FASB standards’ effective dates.

Recently Issued Accounting Pronouncements

From time to time, new accounting pronouncements are issued by the FASB or other standard-setting bodies that the Company adopts as of the specified effective date. The Company qualifies as an “emerging growth company” as defined in the Jumpstart Our Business Startups Act of 2012 and has elected not to “opt out” of the extended transition related to complying with new or revised accounting standards, which means that when a standard is issued or revised and it has different application dates for public and non-public companies, the Company can adopt the new or revised standard at the time non-public companies adopt the new or revised standard and can do so until such time that the

Company either (i) irrevocably elects to "opt out" of such extended transition period or (ii) no longer qualifies as an emerging growth company. The Company may choose to early adopt any new or revised accounting standards whenever such early adoption is permitted for non-public companies. Unless otherwise discussed, the Company believes that the impact of recently issued standards that are not yet effective will not have a material impact on its consolidated financial statements and disclosures.

In February 2016, the FASB issued ASU No. 2016-02, *Leases* (Topic 842), which supersedes all existing lease guidance. This guidance offers specific accounting guidance for a lessee, a lessor and sale and leaseback transactions. The new standard requires lessees to recognize an operating lease with a term greater than one year on their balance sheets as a right-of-use asset and corresponding lease liability, measured at the present value of the lease payments. Lessees are required to classify leases as either finance or operating leases. If the lease is effectively a financed-purchase by the lessee, the lease is classified as a financing lease; otherwise the lease is classified as an operating lease. This classification will determine whether lease expense is recognized based on an effective interest method or on a straight-line basis over the term of the lease. Topic 842 provides accounting guidance for transactions that meet specific criteria for a leaseback transaction. If the criteria are not met, the transaction is considered a "failed sale" and the transaction must be accounted for as a financing arrangement. For EGCs, such as the Company, ASU 2016-02, as amended, will be effective for annual reporting periods beginning after December 15, 2021 and interim periods within those fiscal years, with early adoption permitted. For public entities, ASU No. 2016-02 was effective for annual periods beginning after December 15, 2018, including interim periods within these annual periods. The Company is currently evaluating the full impact that the adoption of ASU 2016-02 is expected to have on its consolidated financial statements; however, the adoption of ASU 2016-02 will require the recognition at the adoption date of both a lease liability, based on the present value of future lease payments, and a corresponding right-to-use asset, which the Company expects to be material. The future lease payment obligation as of December 31, 2021 is disclosed in Note 9, Commitments and Contingencies.

In June 2016, the FASB issued ASU No. 2016-13, *Financial Instruments - Credit Losses* (Topic 326): Measurement of Credit Losses on Financial Instruments. This ASU requires that credit losses for financial instruments measured at amortized cost be reported using an expected losses model rather than the incurred losses model that is currently used, and establishes additional disclosures related to credit risks. For available-for-sale debt securities with unrealized losses, this standard requires allowances to be recorded instead of reducing the amortized cost of the investment. ASU 2016-13 limits the amount of credit losses to be recognized for available-for-sale debt securities to the amount by which carrying value exceeds fair value and requires the reversal of previously recognized credit losses if fair value increases. For EGCs, such as the Company, the new standard will be effective beginning January 1, 2023. For public entities, the standard was effective for fiscal years beginning after December 15, 2019, including interim periods within those fiscal years. The Company is currently evaluating the potential impact this ASU may have on its financial position and results of operations upon adoption.

In December 2019, the FASB issued ASU No. 2019-12, *Income Taxes (Topic 740)—Simplifying the Accounting for Income Taxes* (ASU 2019-12), which is intended to simplify the accounting for income taxes. ASU 2019-12 removes certain exceptions to the general principles in Topic 740 and also clarifies and amends certain aspects of the existing guidance to improve consistent application. For EGCs, such as the Company, ASU 2019-12 is effective beginning January 1, 2022, with early adoption permitted. The Company is currently evaluating the potential impact that this ASU may have on its financial position and results of operations, as well as the timing of its adoption of this standard.

3. Fair Value Measurements

The following tables present the Company's fair value hierarchy for its assets and liabilities that are measured at fair value on a recurring basis and indicate the level within the fair value hierarchy of the valuation techniques the Company utilized to determine such fair value (in thousands):

	Fair Value Measurements at December 31, 2021			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash equivalents				
Money market funds	$ 290,814	$ —	$ —	$ 290,814
Total	$ 290,814	$ —	$ —	$ 290,814

	Fair Value Measurements at December 31, 2020			
	Level 1	Level 2	Level 3	Total
Assets:				
Cash equivalents				
Money market funds	$ 38,795	$ —	$ —	$ 38,795
Total	$ 38,795	$ —	$ —	$ 38,795

Cash and Cash Equivalents—Cash and cash equivalents of $291.1 million and $39.0 million as of December 31, 2021 and December 31, 2020, respectively, consisted of money market funds and are classified within Level 1 of the fair value hierarchy because they are valued using quoted market prices in active markets.

4. Property and Equipment, Net

Property and equipment, net consisted of the following at December 31 (in thousands):

	2021	2020
Laboratory equipment	$ 5,988	$ 2,121
Furniture and fixtures	96	18
Computer equipment	37	22
Leasehold improvements	1,556	1,253
Total property, plant and equipment	7,677	3,414
Less: Accumulated depreciation	(1,416)	(377)
Property, plant and equipment, net	$ 6,261	$ 3,037

Depreciation expense for the years ended December 31, 2021 and 2020 was $1.1 million and $0.3 million, respectively.

5. Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consisted of the following at December 31 (in thousands):

	2021	2020
Employee compensation and benefits	$ 4,077	$ 1,482
External research and development expenses	1,032	125
General and administrative professional service expenses	419	35
Other	485	115
Total accrued expenses and other current liabilities	$ 6,013	$ 1,757

6. Redeemable Convertible Preferred Stock, Common Stock and Preferred Stock

Redeemable Convertible Preferred Stock

Upon the closing of the IPO in November 2021, the Company's Preferred Stock automatically converted into 19,185,183 shares of common stock. As of December 31, 2021, the Company did not have any shares of redeemable convertible preferred stock authorized, issued or outstanding. Redeemable convertible preferred stock consisted of the following at December 31, 2020 (in thousands, except share amounts):

	December 31, 2020				
	Preferred Stock Authorized	Preferred Stock Issued and Outstanding	Carrying Value	Liquidation Preference	Common Stock Issuable Upon Conversion
Series Seed preferred stock	2,420,746	2,420,746	$ 2,061	$ 2,100	334,547
Series A preferred stock	82,879,139	82,879,139	79,597	86,277	11,453,888
	85,299,885	85,299,885	$ 81,658	$ 88,377	11,788,435

On October 27, 2016, the Company entered into a Series Seed Preferred Stock Purchase Agreement, whereby the Company issued an aggregate of 691,641 shares of Series Seed redeemable convertible preferred stock (Series Seed Preferred Stock) at a purchase price of $0.8675 per share for aggregate proceeds of $0.6 million. On March 3, 2017, the Company entered into a second closing of Series Seed Preferred Stock, whereby the Company issued 576,368 shares at a purchase price of $0.8675 per share for aggregate proceeds of $0.5 million. On May 16, 2017, the Company completed the milestone closing of Series Seed Preferred Stock upon the satisfaction of stated milestones pursuant to the Series Seed Preferred Stock Purchase Agreement. In connection with this milestone closing, a total of 1,152,737 shares of Series Seed Preferred Stock were issued at a purchase price of $0.8675, for aggregate gross proceeds of $1.0 million. The Company incurred issuance costs of less than $0.1 million in connection with each of these closings.

On December 14, 2018, the Company entered into a Series A Preferred Stock Purchase Agreement, whereby the Company issued an aggregate of 34,848,403 shares of Series A redeemable convertible preferred stock (Series A Preferred Stock), 24,015,368 of which were issued at a purchase price of $1.041 per share for gross cash proceeds of $25.0 million, and 10,833,035 of which were issued in satisfaction of principal and interest on convertible notes outstanding held by the Company of $9.0 million. Pursuant to the Series A Preferred Stock Purchase Agreement, the Company also agreed to issue up to an additional 24,015,368 shares at a price of $1.041 per share upon the achievement of certain specified milestones.

On January 22, 2020, upon waiver of stated milestones in the Series A Preferred Stock Purchase Agreement, the Company issued 24,015,368 shares of Series A Preferred Stock at a purchase price of $1.041 per share for aggregate proceeds of $25.0 million. The Company incurred issuance costs of less than $0.1 million. Pursuant to the Amended and Restated Series A Preferred Stock Purchase Agreement, on August 12, 2020, the Company agreed to issue an additional 24,015,368 shares of Series A Preferred Stock at a purchase price of $1.041 per share for aggregate proceeds of $25.0 million. The Company incurred issuance costs of $0.1 million.

On March 29, 2021, the Company entered into a Series B Preferred Stock Purchase Agreement, whereby the Company issued an aggregate of 53,522,099 shares of Series B redeemable convertible preferred stock (Series B Preferred Stock, together with the Series Seed Preferred Stock and Series A Preferred Stock, Preferred Stock) at a price of $2.172 per share for gross cash proceeds of $116.2 million. The Company incurred issuance costs of $0.4 million. As part of the issuance of Series B Preferred Stock, the liquidation preferences of the Preferred Stock were modified such that, in the event of any voluntary or involuntary liquidation, dissolution or winding up of the Company or a deemed liquidation event, the holders of Preferred Stock then outstanding shall be entitled to be paid out equal to the greater of (i) the applicable original issue price, plus any dividends declared but unpaid thereon, or (ii) such amount per share as would have been payable had all shares of Preferred Stock been converted into common stock.

The Company amended the articles of incorporation upon the issuance of the Series B Preferred Stock and the rights and preferences of the outstanding shares of Series Seed Preferred Stock and Series A Preferred Stock were adjusted. The Company considered if the adjustment to the previously issued shares of Preferred Stock represents an extinguishment or a modification to the outstanding mezzanine classified instruments. The adjustments to the outstanding shares of Preferred Stock were qualitatively insignificant. As a result, the adjustments to the rights and preferences of the outstanding shares of Preferred Stock qualified as a modification and no accounting was required as holders of these classes of equity did not receive any incremental value in the transaction.

Upon issuance of each class of redeemable convertible preferred stock, the Company assessed the embedded conversion and liquidation features of the shares and determined that such features did not require the Company to separately account for these features. The Company also concluded that no beneficial conversion feature existed on the issuance date of each class of redeemable convertible preferred stock.

Prior to the conversion of the Preferred Stock into shares of common stock upon the completion of the IPO in November 2021, the Preferred Stock had the following rights and preferences:

Conversion Rights

Each share of Preferred Stock is convertible at the option of the holder at any time after the date of issuance. The number of shares of common stock to be issued in the event of a conversion is determined by dividing the original issue price of $0.8675 for the Series Seed Preferred Stock, $1.041 for the Series A Preferred Stock, and $2.172 for the Series B Preferred Stock by the conversion price then in effect. The conversion price for each of the Series Seed Preferred Stock, Series A Preferred Stock, and Series B Preferred Stock was initially $0.8675, $1.041, and $2.172 per share, respectively, subject to adjustment under certain circumstances, including but not limited to certain additional issuances of common shares.

The Preferred Stock automatically convert at either (i) the closing of a firm-commitment underwritten public offering resulting in at least $75 million of net proceeds to the Company, upon which all outstanding Preferred Stock shall automatically be converted into common shares, at the then effective Series Seed conversion price, Series A conversion price, or Series B conversion price, respectively or (ii) at the election of the required majority of Preferred Stock holders, upon which all or any portion of the outstanding Preferred Stock shall automatically be converted into common shares, at the then effective Series Seed conversion price, Series A conversion price, and or Series B conversion price, respectively.

Dividends

The holders of Preferred Stock shall be entitled to receive non-cumulative cash dividends, out of any assets legally available therefor, prior and in preference to any declaration or payment of any dividend on shares of common stock (payable other than in common stock or other securities and rights convertible into or entitling the holder thereof to receive, directly or indirectly, additional shares of common stock of the Company) at a rate of eight percent of the applicable original issue price per share of Preferred Stock per annum, payable only when, as and if declared by the Company's board of directors.

The Company shall not declare, pay or set aside any dividends on shares of any other class or series of capital stock of the Company (other than dividends on shares of common stock payable in shares of common stock) unless (in addition to the obtaining of any consents required otherwise by the Company's restated certificate of incorporation) the holders of Preferred Stock then outstanding shall first receive, or simultaneously receive, in addition to the eight percent non-cumulative dividend described above, a dividend on each outstanding share of Preferred Stock in an amount at least equal to the dividend payable on each share of such class or series determined as if all shares of such class or series had been converted into common stock. No dividends were declared or paid during the years ended December 31, 2021 or 2020.

Liquidation Preference

Upon liquidation, dissolution, or winding up of business or a deemed liquidation event, the holders of the Preferred Stock shall be entitled to be paid out the greater of (i) the applicable original issue price, plus any dividends declared but unpaid thereon, or (ii) such amount per share as would have been payable had all shares of Preferred Stock been converted into common stock. If, upon any such event, the assets available for distribution are insufficient to satisfy the liquidation payment to holders of Preferred Stock in full, the holders of Preferred Stock shall share ratably in any distribution of the assets available for distribution in proportion to the respective amounts which would otherwise be payable in respect of the shares held by them upon such distribution if all amounts payable on or with respect to such shares were paid in full.

Voting Rights

Except as provided by law or by other provisions of the instruments pursuant to which each series of Preferred Stock was issued, holders of the Preferred Stock and common stockholders' vote together as one class on an "as-converted basis." On any matter presented to the stockholders of the Company for their action or consideration at any meeting of stockholders of the Company, each holder of Series Seed Preferred Stock, Series A Preferred Stock, and Series B Preferred Stock is entitled to cast the number of votes equal to the number of whole shares of common stock

into which the shares of Series Seed Preferred Stock, Series A Preferred Stock, and Series B Preferred Stock held by such holder are convertible as of the record date for determining shares entitled to vote on such matter. The holders of the shares of Series A Preferred Stock, exclusively and as a separate class, are entitled to elect three directors of the Company. The holders of the shares of Series B Preferred Stock, exclusively and as a separate class, are entitled to elect one director of the Company. The holders of the shares of common stock and Preferred Stock, exclusively and voting together as a single class, are entitled to elect three directors of the Company.

Common Stock

As of December 31, 2021, the Company's certificate of incorporation, as amended and restated effective upon the completion of the IPO, authorized the Company to issue 150,000,000 shares of common stock, par value $0.0001 per share. The holders of common stock are entitled to one vote for each share held on all matters submitted to a vote of the stockholders. The holders of common stock do not have any cumulative voting rights. Holders of common stock are entitled to receive ratably any dividends declared by the board of directors out of funds legally available for that purpose, subject to any preferential dividend rights of any outstanding preferred stock. Common stock has no preemptive rights, conversion rights or other subscription rights or redemption or sinking fund provisions. In the event of liquidation, dissolution or winding up, holders of common stock will be entitled to share ratably in all assets remaining after payment of all debts and other liabilities and any liquidation preference of any outstanding preferred stock.

As of December 31, 2020, the Company's certificate of incorporation, as amended and restated, authorized the Company to issue 113,259,306 shares of common stock, par value $0.0001 per share. The holders of common stock are entitled to one vote for each share of common stock. Subject to the payment in full of all preferential dividends to which the holders of the Preferred Stock are entitled, the holders of common stock shall be entitled to receive dividends out of funds legally available. In the event of any voluntary or involuntary liquidation, dissolution, or winding up of the Company, after the payment or provision for payment of all debts and liabilities of the Company and all preferential amounts to which the holders of Preferred Stock are entitled with respect to the distribution of assets in liquidation, the holders of common stock shall be entitled to share ratably in the remaining assets of the Company available for distribution.

Shares Reserved for Future Issuance

The Company has reserved the following shares of common stock for future issuance at December 31:

	2021	2020
Exercise of outstanding stock options	3,461,870	1,625,256
Outstanding restricted stock	—	11,537
Future awards under the 2021 Plan	2,843,255	—
Future awards under the 2021 ESPP	278,762	—
Future awards under the 2016 Plan	—	360,306
Conversion of redeemable convertible preferred stock	—	11,788,435
Total shares of authorized common stock reserved for future issuance	6,583,887	13,785,534

Preferred Stock

As of December 31, 2021, the Company was authorized to issue 10,000,000 shares of undesignated preferred stock, $0.0001 par value, in one or more series and to fix the rights, preferences, privileges and restrictions thereof. These rights, preferences and privileges could include dividend rights, conversion rights, voting rights, terms of redemption, liquidation preferences, sinking fund terms and the number of shares constituting, or the designation of, such series, any or all of which may be greater than the rights of common stock. The Company was not authorized to issue any such shares as of December 31, 2020. As of December 31, 2021, there were no shares of undesignated preferred stock issued or outstanding.

7. Stock-Based Compensation

2021 Plan

In September 2021 the Company's board of directors adopted, and in October 2021 the Company's stockholders approved, the 2021 Plan, which became effective as of the date immediately prior to the date of the effectiveness of the registration statement for the IPO. The 2021 Plan allows the board of directors to grant incentive stock options or non-qualified stock options, restricted stock, restricted stock units, and other equity awards to the Company's officers, employees, directors, and other key persons. In addition, the 2021 Plan includes a provision that allows for an automatic annual increase of 4% in the number of shares of common stock available for issuance under the 2021 Plan. The 2021 Plan replaced the 2016 Plan and no additional awards will be granted under the 2016 Plan following the closing of the IPO. The 2016 Plan will continue to govern the outstanding equity awards granted thereunder. The total number of shares of common stock authorized for issuance under the 2021 Plan as of December 31, 2021 was 3,986,270 shares. There were no shares of common stock authorized for issuance under the 2021 Plan as of December 31, 2020.

As of December 31, 2021, the Company had issued only stock options under the 2021 Plan. Stock options issued comprise of service-based awards granted to employees. Vesting of stock options is subject to the recipient's continued employment or service. The maximum term of options granted under the 2021 Plan is ten years, and stock options typically vest over a four-year period.

2021 Employee Stock Purchase Plan

In September 2021, the Company's board of directors adopted, and in October 2021 the Company's stockholders approved, the ESPP, which became effective as of the date immediately prior to the date of the effectiveness of the registration statement for the IPO. The ESPP is administered by the person or persons appointed by the Company's board of directors for such purpose. The ESPP initially provides participating employees with the opportunity to purchase up to an aggregate of 278,762 shares of common stock. The number of shares of common stock reserved for issuance under the ESPP will automatically increase on January 1st of each year beginning in 2022 and continuing through and including 2031 by the least of (i) 1% of the outstanding number of shares of our common stock of the immediately preceding December 31, (ii) 557,524 shares or (iii) such number of shares as determined by the ESPP administrator. As of December 31, 2021, no offering periods have commenced under the 2021 ESPP and 278,762 shares remained available for issuance.

2016 Plan

The 2016 Plan provides for the Company to grant incentive stock options or non-qualified stock options, restricted stock, restricted stock units, and other equity awards to employees, directors, and consultants of the Company. The 2016 Plan is administered by the board of directors of the Company or, at the discretion of the board of directors, by a committee of the board of directors. The exercise prices, vesting, and other restrictions are determined at the discretion of the board of directors, or its committee if so delegated. The 2016 Plan allows for early exercise of all stock option grants if authorized by the board of directors at the time of grant. The shares of common stock issued from the early exercise of stock options are restricted and continue to vest over the original service based vesting condition of the original stock option award. The Company has the option to repurchase any unvested shares at the original purchase price upon any voluntary or involuntary termination.

The total number of shares of common stock authorized for issuance under the 2016 Plan as of December 31, 2021 and 2020 was 2,318,855 shares and 1,997,099 shares, respectively.

Stock-Based Compensation

For the years ended December 31, 2021 and 2020, the Company recorded stock-based compensation expense of $2.5 million and $0.3 million. Stock compensation expense for 2021 and 2020 included less than $0.1 million related to restricted stock in both years and $2.5 million and $0.3 million related to stock options in 2021 and 2020, respectively.

Stock-based compensation expense recorded as research and development and general and administrative expenses in the consolidated statements of operations is as follows (in thousands):

	Year Ended December 31,	
	2021	2020
Research and development expenses	$ 878	$ 107
General and administrative expenses	1,648	218
Total	$ 2,526	$ 325

Stock Option Valuation

The following table presents, on a weighted-average basis, the assumptions used in the Black-Scholes option-pricing model to determine the fair value of stock options granted for the years then ended:

	December 31, 2021	December 31, 2020
Risk-free interest rate	1.15 %	0.53 %
Expected volatility	73 %	75 %
Expected dividend yield	—	—
Expected term (in years)	6.01	5.99

Early Exercise of Unvested Stock Options

Shares purchased by employees pursuant to the early exercise of stock options are not deemed, for accounting purposes, to be outstanding shares until those shares vest according to their respective vesting schedules. Cash received from employee exercises of unvested options is included in current liabilities on the balance sheet. Amounts recorded are reclassified to common stock and additional paid-in capital as the shares vest. Vesting can occur in the year of exercise and thereafter. There were 111,756 and 27,869 unvested shares related to early exercises of stock options as of December 31, 2021 and December 31, 2020, respectively. In the years ended December 31, 2021 and 2020, the liability associated with the unvested early exercise of stock options was $0.3 million and less than $0.1 million, respectively.

Stock Options

The following table summarizes the Company's stock option activity since December 31, 2020:

	Number of Shares	Weighted-Average Exercise Price	Weighted-Average Contractual Term	Aggregate Intrinsic Value (2)
			(in years)	(in thousands)
Outstanding as of December 31, 2020	1,625,256	$ 1.88		
Granted	2,311,485	14.67		
Exercised	(431,687)	2.17		
Forfeited	(43,184)	3.14		
Outstanding as of December 31, 2021	3,461,870	$ 10.38	9.12	$ 26,730
Exercisable as of December 31, 2021 (1)	2,359,876	$ 5.84	8.79	$ 26,730

(1) This represents the number of vested and unvested options exercisable as of December 31, 2021.
(2) The aggregate intrinsic value is calculated as the difference between the exercise price of the underlying options and the estimated fair value of the common stock for the options that were in the money as of December 31, 2021.

The aggregate intrinsic value of stock options exercised during the years ended December 31, 2021 and 2020 was $2.8 million and $0.1 million, while the company received $0.9 million and $0.2 million in proceeds for the exercise of these options, respectively.

The weighted-average grant-date fair value of stock options granted during the years ended December 31, 2021 and 2020 was $9.39 per share and $1.56 per share, respectively. As of December 31, 2021, there was $20.9 million of unrecognized compensation cost related to unvested stock options, which is expected to be recognized over a weighted-average period of 3.5 years.

Restricted Stock Awards

The Company issued restricted stock to its founders and certain officers of the Company. In general, the shares of restricted stock vest over a four-year period, with 25% of the shares vesting after one year, followed by monthly vesting over the remaining three years.

If the holders of the above restricted stock cease to have a business relationship with the Company, the Company may reacquire any unvested shares of restricted stock held by these individuals for the original purchase price or fair value, whichever is lower at the time of repurchase. The amounts received to date for the purchase price of restricted stock are immaterial. The unvested shares of restricted stock are not considered outstanding shares for accounting purposes until the shares vest.

A summary of unvested restricted stock during the year ended December 31, 2021 is as follows:

	Shares	Weighted-Average Grant-Date Fair Value
Unvested as of December 31, 2020	11,537	$ 0.007
Vested	(11,537)	0.007
Unvested as of December 31, 2021	—	$ —

The total fair value of restricted stock vested during each of the years ended December 31, 2021 and 2020 was less than $0.1 million.

8. Income Taxes

For the years ended December 31, 2021 and 2020, the Company recorded no income tax benefits for the net operating losses incurred or for the research and development tax credits generated in each period, due to its uncertainty of realizing a benefit from those items. All of the Company's operating losses since inception have been generated in the United States.

A reconciliation of the U.S. federal statutory income tax rate to the Company's effective income tax rate is as follows:

	Year Ended December 31,	
	2021	2020
Federal statutory income tax rate	21.0 %	21.0 %
State income taxes, net of federal benefit	6.1	6.2
Federal and state research and development tax credits	3.9	4.0
Non-deductible items	(0.3)	(0.2)
Change in deferred tax asset valuation allowance	(30.7)	(31.0)
Effective income tax rate	— %	— %

Net deferred tax assets as of December 31, 2021 and 2020 consisted of the following (in thousands):

	December 31,	
	2021	2020
Deferred tax assets:		
Net operating loss carryforwards	$ 25,124	$ 11,214
Research and development tax credit carryforwards	3,237	1,236
Intangible assets	761	432
Salaries and wages	—	313
Stock compensation	430	80
Other	137	76
Total deferred tax assets	29,689	13,351
Deferred tax liabilities:		
Property and equipment	(261)	(111)
Prepaid expenses	(485)	—
Total deferred tax liabilities	(746)	(111)
Valuation allowance	(28,943)	(13,240)
Net deferred tax assets	$ —	$ —

As of December 31, 2021, the Company had federal net operating loss carryforwards of $93.1 million, which may be available to offset future taxable income, of which $3.2 million of the total net operating loss carryforwards expire at various dates beginning in 2036, while the remaining $89.9 million do not expire but are limited in their usage to an annual deduction equal to 80% of annual taxable income. In addition, as of December 31, 2021, the Company had state net operating loss carryforwards of $88.0 million, which may be available to offset future taxable income and expire at various dates beginning in 2036. As of December 31, 2021, the Company also had federal and state research and development tax credit carryforwards of $2.3 million and $1.2 million, respectively, which may be available to reduce future tax liabilities and expire at various dates beginning in 2039 and 2034, respectively.

Utilization of the U.S. federal and state net operating loss carryforwards and research and development tax credit carryforwards may be subject to a substantial annual limitation under Section 382 and Section 383 of the Internal Revenue Code of 1986 (Code), and corresponding provisions of state law, 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 and tax liabilities. In general, an ownership change, as defined by Section 382 of the Code, results from transactions increasing the ownership of certain stockholders or public groups in the stock of a corporation by more than 5% over a three-year period. The Company has not conducted a study to assess whether a change of control has occurred or whether there have been multiple changes of control since inception due to the significant complexity and cost associated with such a study. If the Company has experienced a change of control, as defined by Section 382 of the Code, at any time since inception, utilization of the net operating loss carryforwards or research and development tax credit carryforwards may be subject to an annual limitation, which is determined by first multiplying the value of the Company's stock at the time of the ownership change by the applicable long-term tax-exempt rate, and then could be subject to additional adjustments. Any limitation may result in expiration of a portion of the net operating loss carryforwards or research and development tax credit carryforwards before their utilization. Further, until a study is completed by the Company and any limitation is known, no amounts are being presented as an uncertain tax position.

The Company has evaluated the positive and negative evidence bearing upon its ability to realize the deferred tax assets, which consist primarily of net operating loss carryforwards and research and development tax credit carryforwards. Management has considered the Company's history of cumulative net losses incurred since inception, estimated future taxable income, and prudent and feasible tax planning strategies and has concluded that it is more likely than not that the Company will not realize the benefits of federal and state net deferred tax assets. Accordingly, a full valuation allowance has been established against the net deferred tax assets as of December 31, 2021 and 2020. The Company reevaluates the positive and negative evidence at each reporting period.

The valuation allowance increased by $15.7 million and $8.2 million for the year ending December 31, 2021 and 2020, respectively. The increase in the valuation allowance for deferred tax assets during the years ended December 31, 2021 and 2020 related primarily to the increases in net operating loss carryforwards and research and development tax credit carryforwards.

The Company assesses the uncertainty in its income tax positions to determine whether a tax position of the Company is more likely than not to be sustained upon examination, including resolution of any related appeals of litigation processes, based on the technical merits of the position. For tax positions meeting the more-likely-than-not threshold, the tax amount recognized in the consolidated financial statements is reduced by the largest benefit that has a greater than 50% likelihood of being realized upon the ultimate settlement with the relevant taxing authority. The Company's policy is to recognize interest and penalties accrued on any uncertain tax positions as a component of income tax expense, if any, in its consolidated statements of operations. As of December 31, 2021 and 2020, the Company had not recorded any reserves for uncertain tax positions or related interest and penalties.

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 federal and state jurisdictions, where applicable. Due to net operating losses incurred, the Company's tax returns from inception to date are subject to examination by the taxing authorities.

9. Commitments and Contingencies

Lease Obligations

In March 2019, the Company entered into an operating lease for 7,981 square feet of office and laboratory space with an end date of April 30, 2021 in Boston, Massachusetts. The Company subsequently terminated the operating lease in December 2020 without penalty.

In February 2020, the Company entered into an operating lease for 26,235 square feet of office and laboratory space in Boston, Massachusetts. Lease payments commenced in April 2020. The lease is subject to fixed rate escalation increases. The Company recognizes rent expense on a straight-line basis over the expected lease term, which is 5.7 years. The Company began to record rent expense in April 2020 upon gaining access to and control of the space. Deferred rent is amortized as a reduction in rent expense over the term of the lease. In addition, upon execution of the lease, the Company paid a security deposit of approximately $0.5 million, which is recorded as a component of other assets in the accompanying consolidated balance sheets as of December 31, 2021 and 2020. The Company has the option to terminate the lease after November 30, 2023 without penalty.

In June 2021, the Company entered into amendments to the operating lease for 8,631 square feet of additional office and laboratory space at its location in Boston, Massachusetts. The term of the amendments begin between July 2021 and March 2022 and run co-terminus with the existing lease. The Company has the same option to terminate the lease after November 30, 2023 without penalty. The Company was required to increase its total security deposit to $0.8 million as of the commencement date of the amendments.

The Company recorded $6.0 million and $1.9 million of rent expense for the years ended December 31, 2021 and 2020, respectively.

The minimum aggregate future lease commitments at December 31, 2021, are as follows (in thousands):

Years Ending December 31,		
2022	$	8,526
2023		8,384
Total future lease payments	$	16,910

License Agreement

In 2017, the Company entered into an option agreement with a third party, in which the Company obtained an option to license all patents and patent applications specified in the agreement, involving work related to specified invention disclosures, and arising out of that sponsored research agreement entered into between the Company and such third party pursuant to which the Company sponsored certain discovery programs conducted by the third party. In 2018, the Company entered into a definitive license agreement with the third party in which the third party granted the Company an exclusive worldwide, sublicensable license to certain intellectual property under certain patent rights to research, develop, and otherwise commercialize a product generated from the licensed intellectual property. The Company concluded the assets acquired did not meet the accounting definition of a business as inputs, but no processes

or outputs were acquired with the licenses. As the inputs that were acquired along with the licenses do not constitute a "business," the transaction has been accounted for as an asset acquisition under ASC 730. As of the date of the license agreement, the assets acquired had no alternative future use and the assets had not reached a stage of technological feasibility. The Company paid an upfront research fee of $0.4 million, paid in two installments of $0.2 million on June 30, 2019 and June 30, 2020, respectively, which were accrued and recognized as research and development expense in 2018. The Company agreed to pay an annual license maintenance fee for the license of less than $0.1 million for each contract year, beginning the third year of the contract until the first commercial contract year. The Company also issued a total of 86,558 shares of common stock pursuant to the 2018 agreement, which were recorded at fair value at the date of issuance of $0.2 million.

Should the Company pursue specified research, development, and commercial activities related to the above technology, the Company would be obligated to make milestone payments up to $2.6 million for each of the first three licensed products to achieve each milestone. The triggering of these milestone payments was not considered probable as of the transaction date, and no expense has been recorded for these milestones as of December 31, 2021 and 2020. In addition, the third party will receive tiered royalty payments on the applicable licensed program and platform products at a percentage ranging in single-digit royalties of net sales subject to reductions and offsets in certain circumstances, as well as a royalty on sublicensed consideration ranging from low to mid double-digit percentages of non-royalty sublicensing consideration. The Company concluded any milestone or royalty payments under the agreement were not probable as of December 31, 2021 and 2020. For each of the years ended December 31, 2021 and 2020, the Company reimbursed the third-party for patent costs of $0.1 million.

10. Employee Benefit Plan

The Company has a defined-contribution plan under Section 401(k) of the Code (401(k) Plan). The 401(k) Plan covers all employees who meet defined minimum age and service requirements and allows participants to defer a portion of their annual compensation on a pre-tax basis. As currently established, the Company is not required to make, and to date has not made, any contributions to the 401(k) Plan.

11. Net Loss per Share

Basic and diluted net loss per share attributable to common stockholders was calculated as follows (in thousands, except share and per share amounts):

	Year Ended December 31,	
	2021	2020
Numerator:		
Net loss attributable to common stockholders	$ (51,158)	$ (26,523)
Denominator:		
Weighted-average common shares outstanding, basic and diluted	6,267,776	1,105,260
Net loss per share attributable to common stockholders, basic and diluted	$ (8.16)	$ (24.00)

Common Stock Equivalents

The Company excluded the following potential common shares, presented based on amounts outstanding at each period end, from the computation of diluted net loss per share attributable to common stockholders for the periods indicated because including them would have had an anti-dilutive effect:

	Year Ended December 31,	
	2021	2020
Redeemable convertible preferred stock (as converted to common stock)	—	11,788,435
Unvested restricted common stock	—	11,537
Unvested shares from early exercises	111,756	27,869
Stock options to purchase common stock	3,461,870	1,625,256
	3,573,626	13,453,097

12. Subsequent Events

For the year ended December 31, 2021, subsequent events were evaluated through the date on which these consolidated financial statements were issued to determine if such events should be reflected in these consolidated financial statements. The Company has concluded that no subsequent events have occurred that require disclosure.

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

None.

Item 9A. Controls and Procedures

Evaluation of Disclosure Controls and Procedures

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Our management, with the participation of our Chief Executive Officer and our Chief Financial Officer (our principal executive officer and principal financial and accounting officer, respectively), evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2021. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended (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 Securities and Exchange Commission (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 the company's management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure.

Our 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, 2021, our Chief Executive Officer and our Chief Financial Officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Annual Report on Internal Control Over Financial Reporting

This Annual Report does not include a report of management's assessment regarding internal control over financial reporting due to a transition period established by the rules of the SEC for newly public companies.

Attestation Report of the Registered Public Accounting Firm

This Annual Report does not include an attestation report of our registered public accounting firm due to an exemption provided by the JOBS Act for "emerging growth companies."

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during the quarter ended December 31, 2021 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections

Not Applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance

The information required by this Item 10 will be included in our definitive proxy statement relating to our 2022 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year, and is incorporated herein by reference.

Item 11. Executive Compensation

The information required by this Item 11 will be included in our definitive proxy statement relating to our 2022 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year, and is incorporated herein by reference.

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

The information required by this Item 12 will be included in our definitive proxy statement relating to our 2022 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year, and is incorporated herein by reference.

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

The information required by this Item 13 will be included in our definitive proxy statement relating to our 2022 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year, and is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services

The information required by this Item 14 will be included in our definitive proxy statement relating to our 2022 Annual Meeting of Stockholders, which we will file with the SEC within 120 days of the end of the fiscal year, and is incorporated herein by reference.

PART IV

Item 15. Exhibits and Financial Statement Schedules

(a) Exhibits

Exhibit Number	Description
3.1	Fourth Amended and Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to the Current Report on Form 8-K filed by the Registrant on November 2, 2021).
3.2	Amended and Restated Bylaws of the Registrant (incorporated by reference to Exhibit 3.2 to the Current Report on Form 8-K filed by the Registrant on November 2, 2021).
4.1	Specimen Common Stock Certificate (incorporated by reference to Exhibit 4.1 to the Registration Statement on Form S-1 filed by the Registrant on October 25, 2021).
4.2	Amended and Restated Investors' Rights Agreement among the Registrant and certain of its stockholders, effective as of March 29, 2021 (incorporated by reference to Exhibit 4.2 to the Registration Statement on Form S-1 filed by the Registrant on October 8, 2021).
4.3*	Description of Securities of the Registrant
10.1#	2021 Stock Option and Incentive Plan and form of award agreements thereunder (incorporated by reference to Exhibit 10.2 to the Registration Statement on Form S-1 filed by the Registrant on October 25, 2021).
10.2#	2021 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.3 to the Registration Statement on Form S-1 filed by the Registrant on October 25, 2021).
10.3#	Form of Indemnification Agreement between the Registrant and each of its directors (incorporated by reference to Exhibit 10.4 to the Registration Statement on Form S-1 filed by the Registrant on October 25, 2021).
10.4#	Form of Indemnification Agreement between the Registrant and each of its executive officers (incorporated by reference to Exhibit 10.5 to the Registration Statement on Form S-1 filed by the Registrant on October 25, 2021).
10.5#	Senior Executive Cash Incentive Bonus Plan (incorporated by reference to Exhibit 10.6 to the Registration Statement on Form S-1 filed by the Registrant on October 25, 2021).
10.6#	Form of Executive Employment Agreement (incorporated by reference to Exhibit 10.7 to the Registration Statement on Form S-1 filed by the Registrant on October 25, 2021).
10.7#	Non-Employee Director Compensation Policy (incorporated by reference to Exhibit 10.8 to the Registration Statement on Form S-1 filed by the Registrant on October 25, 2021).
10.8#	Amended and Restated Employment Agreement, by and between the Registrant and Dipal Doshi, effective as of November 2, 2021 (incorporated by reference to Exhibit 10.9 to the Registration Statement on Form S-1 filed by the Registrant on October 25, 2021).
10.9#	Amended and Restated Employment Agreement, by and between the Registrant and Natarajan Sethuraman, effective as of November 2, 2021 (incorporated by reference to Exhibit 10.10 to the Registration Statement on Form S-1 filed by the Registrant on October 25, 2021).
10.10#	Amended and Restated Employment Agreement, by and between the Registrant and Nathan Dowden, effective as of November 2, 2021 (incorporated by reference to Exhibit 10.11 to the Registration Statement on Form S-1 filed by the Registrant on October 25, 2021).
10.11#	Amended and Restated Strategic Advisory Agreement, by and between the Registrant and Peter S. Kim, effective as of November 2, 2021 (incorporated by reference to Exhibit 10.12 to the Registration Statement on Form S-1 filed by the Registrant on October 25, 2021).
10.12†	Exclusive License Agreement, by and between the Registrant and OSIF, dated as of December 14, 2018, as amended on October 8, 2019 and further amended on March 9, 2019 (incorporated by reference to Exhibit 10.13 to the Registration Statement on Form S-1 filed by the Registrant on October 8, 2021).

10.13	License Agreement, dated as of February 28,2020, by and between the Registrant and MIL 6T, LLC, as amended on March 27, 2020 (incorporated by reference to Exhibit 10.14 to the Registration Statement on Form S-1 filed by the Registrant on October 8, 2021).
21.1*	List of Subsidiaries of the Registrant.
23.1*	Consent of Ernst & Young LLP, independent registered public accounting firm.
24.1*	Power of Attorney (included on signature page).
31.1*	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2*	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1*+	Certifications of Principal Executive Officer and Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101.INS	Inline XBRL Instance Document – the instance document does not appear in the Interactive Data File because XBRL tags are embedded within the Inline XBRL document.
101.SCH	Inline XBRL Taxonomy Extension Schema Document.
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document.
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document.
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document.
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document.
104	Cover Page Interactive Data File (embedded within the Inline XBRL document).

* Filed or furnished herewith.

† Portions of this exhibit (indicated by asterisks) have been omitted in accordance with Item 601(b)(10) of Regulation S-K.

# Indicates a management contract or any compensatory plan, contract or arrangement.

+ The certifications furnished in Exhibit 32.1 hereto are deemed to be furnished with this Annual Report and will not be deemed to be “filed” for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, except to the extent that the Registrant specifically incorporates it by reference.

(b) Financial Statements Schedules

Schedules have been omitted because the information required to be set forth therein is not applicable or is shown in the consolidated financial statements or notes thereto.

Item 16. Form 10-K Summary

Not applicable.

SIGNATURES

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

Date: March 15, 2022

ENTRADA THERAPEUTICS, INC.

By: /s/ Dipal Doshi
Name: Dipal Doshi
Title: President and Chief Executive Officer
(Principal Executive Officer)

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose individual signature appears below hereby authorizes and appoints Dipal Doshi and Kory Wentworth, and each of them, with full power of substitution and re-substitution and full power to act without the other, 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 Annual Report on Form 10-K and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing, ratifying and confirming all that said attorneys-in-fact and agents or any of them or their 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 Annual Report on Form 10-K has been signed below by the following persons on behalf of the registrant and in the capacities and on the date indicated.

Name	Title	Date
/s/ Dipal Doshi Dipal Doshi	President and Chief Executive Officer *(Principal Executive Officer)*	March 15, 2022
/s/ Kory Wentworth Kory Wentworth	Chief Financial Officer (*Principal Financial and Accounting Officer)*	March 15, 2022
/s/ Kush M. Parmar, M.D., Ph.D. Kush M. Parmar, M.D., Ph.D.	Chairman and Director	March 15, 2022
/s/ John F. Crowley John F. Crowley	Director	March 15, 2022
/s/ Todd Foley Todd Foley	Director	March 15, 2022
/s/ Peter S. Kim, Ph.D. Peter S. Kim, Ph.D.	Director	March 15, 2022
/s/ Carole Nuechterlein Carole Nuechterlein	Director	March 15, 2022
/s/ Mary Thistle Mary Thistle	Director	March 15, 2022

DESCRIPTION OF THE REGISTRANT'S SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES AND EXCHANGE ACT OF 1934, AS AMENDED

The following description of the capital stock of Entrada Therapeutics, Inc., a Delaware corporation (the "Company," "we," "us," and "our"), is a summary of certain provisions of our securities that are registered under Section 12 of the Securities and Exchange Act of 1934, as amended (the "Exchange Act"), and does not purport to be complete. It is subject to and qualified in its entirety by reference to our Fourth Amended and Restated Certificate of Incorporation (as amended and/or restated from time to time, the "Certificate of Incorporation") and our Amended and Restated Bylaws (as amended and/or restated from time to time, the "Bylaws"), each of which is incorporated by reference as an exhibit to the Annual Report on Form 10-K of which this Exhibit 4.3 is a part, and by applicable law. This description also summarizes relevant provisions of the General Corporation Law of the State of Delaware (the "DGCL"). We encourage you to read our Certificate of Incorporation, our Bylaws and the applicable provisions of the DGCL for additional information.

Authorized Capital Stock

The total amount of our authorized capital stock consists of 150,000,000 shares of common stock, par value $0.0001 per share, and 10,000,000 shares of preferred stock, par value $0.0001 per share, all of which shares of preferred stock are undesignated.

Common Stock

The holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of the stockholders. The holders of our common stock do not have any cumulative voting rights. Holders of our common stock are entitled to receive ratably any dividends declared by our board of directors out of funds legally available for that purpose, subject to any preferential dividend rights of any outstanding preferred stock. Our common stock has no preemptive rights, conversion rights or other subscription rights or redemption or sinking fund provisions.

In the event of our liquidation, dissolution or winding up, holders of our common stock will be entitled to share ratably in all assets remaining after payment of all debts and other liabilities and any liquidation preference of any outstanding preferred stock. Each outstanding share of common stock is fully paid and non-assessable.

Preferred Stock

Our board of directors will have the authority, without further action by our stockholders, to issue up to 10,000,000 shares of preferred stock in one or more series and to fix the rights, preferences, privileges and restrictions thereof. These rights, preferences and privileges could include dividend rights, conversion rights, voting rights, terms of redemption, liquidation preferences, sinking fund terms and the number of shares constituting, or the designation of, such series, any or all of which may be greater than the rights of common stock. The issuance of our preferred stock could adversely affect the voting power of holders of common stock and the likelihood that such holders will receive dividend payments and payments upon our liquidation. In addition, the issuance of preferred stock could have the effect of delaying, deferring or preventing a change in control of our Company or other corporate action.

No shares of preferred stock are outstanding as of the date of our Annual Report on Form 10-K with which this Exhibit 4.3 is filed as an exhibit.

Anti-Takeover Effects of Delaware Law and Provisions of our Charter and our Bylaws

Certain provisions of the DGCL and of our Certificate of Incorporation and Bylaws could have the effect of delaying, deferring or preventing another party from acquiring control of us and encouraging persons considering unsolicited tender offers or other unilateral takeover proposals to negotiate with our board of directors rather than pursue non-negotiated takeover attempts. These provisions include the items described below.

Board Composition and Filling Vacancies

Our Certificate of Incorporation provides for the division of our board of directors into three classes serving staggered three-year terms, with one class being elected each year. Our Certificate of Incorporation also provides that

directors may be removed only for cause and then only by the affirmative vote of the holders of two-thirds or more of the shares then entitled to vote at an election of directors. Furthermore, any vacancy on our board of directors, however occurring, including a vacancy resulting from an increase in the size of our board of directors, may only be filled by the affirmative vote of a majority of our directors then in office even if less than a quorum. The classification of directors, together with the limitations on removal of directors and treatment of vacancies, has the effect of making it more difficult for stockholders to change the composition of our board of directors.

No Written Consent of Stockholders

Our Certificate of Incorporation provides that all stockholder actions are required to be taken by a vote of the stockholders at an annual or special meeting, and that stockholders may not take any action by written consent in lieu of a meeting. This limit may lengthen the amount of time required to take stockholder actions and would prevent the amendment of our Bylaws or removal of directors by our stockholders without holding a meeting of stockholders.

Meetings of Stockholders

Our Certificate of Incorporation and Bylaws provide that only a majority of the members of our board of directors then in office may call special meetings of stockholders and only those matters set forth in the notice of the special meeting may be considered or acted upon at a special meeting of stockholders. Our Bylaws limit the business that may be conducted at an annual meeting of stockholders to those matters properly brought before the meeting.

Advance Notice Requirements

Our Bylaws establish advance notice procedures with regard to stockholder proposals relating to the nomination of candidates for election as directors or new business to be brought before meetings of our stockholders. These procedures provide that notice of stockholder proposals must be timely given in writing to our corporate secretary prior to the meeting at which the action is to be taken. Generally, to be timely, notice must be received at our principal executive offices not less than 90 days nor more than 120 days prior to the first anniversary date of the annual meeting for the preceding year. Our Bylaws specify the requirements as to form and content of all stockholders' notices. These requirements may preclude stockholders from bringing matters before the stockholders at an annual or special meeting.

Amendment to Certificate of Incorporation and Bylaws

Any amendment of our Certificate of Incorporation must first be approved by a majority of our board of directors, and if required by law or our Certificate of Incorporation, must thereafter be approved by a majority of the outstanding shares entitled to vote on the amendment and a majority of the outstanding shares of each class entitled to vote thereon as a class, except that the amendment of the provisions relating to stockholder action, board composition, and limitation of liability must be approved by not less than two-thirds of the outstanding shares entitled to vote on the amendment, and not less than two-thirds of the outstanding shares of each class entitled to vote thereon as a class. Our Bylaws may be amended by the affirmative vote of a majority of the directors then in office, subject to any limitations set forth in the Bylaws; and may also be amended by the affirmative vote of a majority of the outstanding shares entitled to vote on the amendment, voting together as a single class, except that the amendment of the provisions relating to notice of stockholder business and nominations and special meetings must be approved by not less than two-thirds of the outstanding shares entitled to vote on the amendment, and not less than two-thirds of the outstanding shares of each class entitled to vote thereon as a class, or, if our board of directors recommends that the stockholders approve the amendment, by the affirmative vote of the majority of the outstanding shares entitled to vote on the amendment, in each case voting together as a single class.

Undesignated Preferred Stock

Our Certificate of Incorporation provides for 10,000,000 authorized shares of preferred stock. The existence of authorized but unissued shares of preferred stock may enable our board of directors to discourage an attempt to obtain control of us by means of a merger, tender offer, proxy contest or otherwise. For example, if in the due exercise of its fiduciary obligations, our board of directors were to determine that a takeover proposal is not in the best interests of our stockholders, our board of directors could cause shares of preferred stock to be issued without stockholder approval in one or more private offerings or other transactions that might dilute the voting or other rights of the proposed acquirer or insurgent stockholder or stockholder group. In this regard, our Certificate of Incorporation grants our board of directors broad power to establish the rights and preferences of authorized and unissued shares of

preferred stock. The issuance of shares of preferred stock could decrease the amount of earnings and assets available for distribution to holders of shares of common stock. The issuance may also adversely affect the rights and powers, including voting rights, of these holders and may have the effect of delaying, deterring or preventing a change in control of us.

Choice of Forum

Our Bylaws provide that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware shall be the sole and exclusive forum for any state law claims for (1) any derivative action or proceeding brought on our behalf, (2) any action asserting a claim of breach of a fiduciary duty owed by any of our directors, officers, and employees to us or our stockholders, (3) any action asserting a claim arising pursuant to the DGCL, our Certificate of Incorporation or our Bylaws, (4) any action to interpret, apply, enforce or determine the validity of our Certificate of Incorporation or our Bylaws, or (5) any action asserting a claim that is governed by the internal affairs doctrine; provided, however, that the this provision shall not apply to any causes of action arising under the Securities Act or Exchange Act. In addition, our Bylaws provide that, unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States shall be the sole and exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act. Any person or entity purchasing or otherwise acquiring any interest in our securities shall be deemed to have notice of and consented to these forum provisions. These forum provisions may impose additional costs on stockholders, may limit our stockholders' ability to bring a claim in a forum they find favorable, and the designated courts may reach different judgments or results than other courts. In addition, there is uncertainty as to whether the federal forum provision for Securities Act claims will be enforced, which may impose additional costs on us and our stockholders.

Section 203 of the Delaware General Corporation Law

We are subject to the provisions of Section 203 of the DGCL. In general, Section 203 prohibits a publicly held Delaware corporation from engaging in a "business combination" with an "interested stockholder" for a three-year period following the time that this stockholder becomes an interested stockholder, unless the business combination is approved in a prescribed manner. Under Section 203, a business combination between a corporation and an interested stockholder is prohibited unless it satisfies one of the following conditions:

Section 203 defines a business combination to include:

- before the stockholder became interested, our board of directors approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;

- upon consummation of the transaction which resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the voting stock outstanding, shares owned by persons who are directors and also officers, and employee stock plans, in some instances, but not the outstanding voting stock owned by the interested stockholder; or

- at or after the time the stockholder became interested, the business combination was approved by our board of directors and authorized at an annual or special meeting of the stockholders by the affirmative vote of at least two-thirds of the outstanding voting stock which is not owned by the interested stockholder.

Section 203 defines a business combination to include:

- any merger or consolidation involving the corporation and the interested stockholder;

- any sale, transfer, lease, pledge or other disposition involving the interested stockholder of 10% or more of the assets of the corporation;

- subject to exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;

- subject to exceptions, any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of any class or series of the corporation beneficially owned by the interested stockholder; and

- the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges, or other financial benefits provided by or through the corporation.

In general, Section 203 defines an interested stockholder as any entity or person beneficially owning 15% or more of the outstanding voting stock of the corporation and any entity or person affiliated with or controlling or controlled by the entity or person.

Stock Exchange Listing

Our common stock is listed on the Nasdaq Global Market under the trading symbol “TRDA.”

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is Computershare Trust Company, N.A.

Exhibit 21.1

SUBSIDIARIES

Subsidiary	**Jurisdiction of Incorporation**
Entrada Securities Corporation	Massachusetts

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the Registration Statement (Form S-8 No. 333-260563) pertaining to the 2021 Stock Option and Incentive Plan, the 2021 Employee Stock Purchase Plan and the 2016 Stock Incentive Plan of Entrada Therapeutics, Inc. of our report dated March 15, 2022, with respect to the consolidated financial statements of Entrada Therapeutics, Inc. included in this Annual Report (Form 10-K) of Entrada Therapeutics, Inc. for the year ended December 31, 2021.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 15, 2022

Exhibit 31.1

CERTIFICATION PURSUANT TO
RULES 13a-14(a) OR 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Dipal Doshi, certify that:

1. I have reviewed this Form 10-K for the Annual Period Ended December 31, 2021 of Entrada Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(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)) 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. (Paragraph omitted pursuant to SEC Release Nos. 33-8238/34-47986 and 33-8392/34-49313);

    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 15, 2022

By: /s/ Dipal Doshi

Dipal Doshi
President and Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATION PURSUANT TO
RULES 13a-14(a) OR 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Kory Wentworth, certify that:

1. I have reviewed this Form 10-K for the Annual Period Ended December 31, 2021 of Entrada Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer(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)) 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. (Paragraph omitted pursuant to SEC Release Nos. 33-8238/34-47986 and 33-8392/34-49313);

    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 15, 2022

By: /s/ Kory Wentworth

Kory Wentworth
Chief Financial Officer
(Principal Financial and Accounting Officer)

Exhibit 32.1

CERTIFICATIONS OF PRINCIPAL EXECUTIVE OFFICER AND PRINCIPAL FINANCIAL OFFICER PURSUANT TO 18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of Entrada Therapeutics, Inc. (the "Company") for the fiscal year ended December 31, 2021 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned hereby certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that, to the best of their knowledge:

(1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Date: March 15, 2022

By: /s/ Dipal Doshi

Dipal Doshi
President and Chief Executive Officer
(Principal Executive Officer)

Date: March 15, 2022

By: /s/ Kory Wentworth

Kory Wentworth
Chief Financial Officer
(Principal Financial and Accounting Officer)