**Risk Factors Comparison 2025-03-11 to 2024-02-28 Form: 10-K**

**Legend:** **New Text** ~~Removed Text~~ Unchanged Text Moved Text Section

Risks Related to Our Financial Position and Need for Capital We have a history of incurring significant losses and anticipate that we will continue to incur losses for the foreseeable future and may never achieve or maintain consistent profitability. We are an early- stage biotechnology company and have not yet generated revenues from the sales of our product candidates. All of our product candidates are in the early stages of development. Investment in biotechnology companies is highly speculative because it entails substantial upfront capital expenditures and significant risk that any product candidates will fail to be safe and efficacious, obtain regulatory approval or become commercially viable. We have not yet demonstrated the ability to complete any clinical trials of our product candidates, obtain marketing approvals, manufacture a commercial- scale product or conduct sales and marketing activities necessary for successful commercialization. We continue to incur significant expenses related to research and development, and other operations in order to commercialize our product candidates. We have a history of incurring significant operating losses. We had **a net loss of $ 65. 0 million,** net income of $ 132. 3 million **,** and **a** net ~~losses~~ **loss** of $ 46. 4 million for the years ended December 31, **2024,** 2023 **,** and **2022, respectively. As of** December 31, ~~2022~~ **2024** ~~, respectively. As of December 31, 2023~~, we had an accumulated deficit of $ ~~261~~ **326** . 2 million. We historically have financed our operations primarily through private placements of our redeemable convertible preferred stock, public offerings and private placements of our common stock, and strategic collaborations, including our prior collaborations with Sanofi Genzyme Corporation, or Sanofi Genzyme, AbbVie Biotechnology Ltd and AbbVie Ireland Unlimited Company, and our ongoing collaborations with Neurocrine Biosciences, Inc., or Neurocrine, and Novartis Pharma AG, or Novartis; our option and license agreement, or the Alexion Agreement, with Alexion, AstraZeneca Rare Disease, or Alexion; and our option and license agreement, or the 2022 Novartis Option and License Agreement, with Novartis. We refer to our ongoing collaborations with Neurocrine collectively as the Neurocrine Collaborations. To date, we have devoted substantially all of our financial resources to building our gene therapy **and non- viral therapeutics** ~~platform~~ **platforms** , selecting product programs, conducting research and development, including preclinical **and clinical** development of our product candidates, building our intellectual property portfolio, building our team, and establishing strategic collaborations. We expect that it could be several years before we have a commercialized product, if ever. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. We also anticipate the cost of goods and services **,** and the levels of compensation paid to employees will increase due to inflationary conditions existing in the general economy. The net losses we incur may fluctuate significantly from quarter to quarter. We anticipate that our expenses will increase substantially if, and as, we: ● conduct ~~preclinical development activities and initiate investigational new drug, or IND, application- enabling studies and~~ clinical trials in connection with our anti- tau antibody program ~~and our SOD1 ALS gene therapy program~~ ; ● continue investing in our proprietary antibody program, **non- viral therapeutics platform,** gene therapy and vectorized antibody platforms and programs, and other research and development initiatives; ● **continue investing** ~~increase our investment~~ in and ~~support~~ **supporting** ~~for TRACERTM~~ **TRACER ™** (Tropism Redirection of AAV by Cell ~~Type~~ **type- Specific specific** Expression of RNA), our proprietary discovery platform to facilitate the selection of adeno- associated virus, or AAV, capsids **, which we refer to as TRACER Capsids,** and ~~expand~~ our investment to discover TRACER Capsids with broad tropism in ~~central nervous system, or~~ CNS and other tissues with cell- specific transduction properties for particular therapeutic applications; ● increase our investment in the discovery and development of modalities for receptor- mediated non- viral delivery of therapeutic payloads to the CNS; ● conduct joint research and development under our strategic collaborations for the research, development, and commercialization of certain of our pipeline programs, including our ~~FXN gene therapy program for~~ Friedreich' s ataxia **program** , or the FA Program, pursuant to our collaboration and license agreement with Neurocrine entered into in January 2019, or the 2019 Neurocrine Collaboration Agreement ~~;~~ **,** our ~~glucocerebrosidase~~ **glucosylceramidase beta** 1, or GBA1, gene therapy program for Parkinson' s disease and other GBA1- mediated diseases, or the GBA1 Program, pursuant to our collaboration and license agreement with Neurocrine entered into ~~on~~ **in** January ~~8,~~ 2023, or the 2023 Neurocrine Collaboration Agreement ~~;~~ **,** and our Huntington' s disease program, or the Novartis HD Program **,** pursuant to our license and collaboration agreement with Novartis entered into ~~on~~ **in** December ~~28,~~ 2023, or the 2023 Novartis Collaboration Agreement; ● initiate additional preclinical studies and clinical trials for, and continue research and development of, our other programs; ● continue our process research and development activities, as well as establish our research- grade manufacturing capabilities; ● identify additional diseases for treatment with our AAV gene therapies and develop additional programs or product candidates; ~~50~~ ● seek marketing and regulatory approvals for any of our product candidates that successfully complete clinical development; ● maintain, expand, protect and enforce our intellectual property portfolio; ● identify, acquire or in- license other product candidates and technologies; ● expand our operational, financial and management systems and personnel, including personnel to support our clinical development, manufacturing and commercialization efforts; ● ~~continue~~ **increase** our clinical trial insurance coverage as we expand our clinical trials and increase our product liability insurance once we engage in commercialization efforts; and ● continue to operate as a public company. Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses. Our expenses will increase if: ● we are required by the U. S. Food and Drug Administration, or the FDA, or the European Medicines Agency, or EMA, or other regulatory agencies to redesign or modify trials or studies or to perform trials or studies in addition to those currently expected; ● there are any delays in the receipt of regulatory clearance to begin our planned clinical programs; or ● there are any delays in enrollment of patients in or completing our clinical trials or the development of our product candidates.

~~To~~ **51To** become and remain profitable, we must develop and commercialize, alone or with our collaborators, product candidates with significant market potential, which will require us to be successful in a range of challenging activities. These activities include completing preclinical studies and clinical trials of our product candidates; obtaining marketing approval for these product candidates; contracting with third parties with expertise in current good manufacturing practices, or cGMPs, to manufacture our product candidates at clinical and commercial scale; marketing and selling those products that are approved; satisfying any post- marketing requirements and achieving an adequate level of market acceptance of and obtaining and maintaining adequate coverage and reimbursement from third- party payors for such products; and protecting our rights to our intellectual property portfolio. We may never succeed in any or all of these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our company also could cause our stockholders to lose all or part of their investment. We may not be able to generate sufficient revenue from the commercialization of our product candidates and may never be consistently profitable. Our ability to generate revenue and achieve profitability depends on our ability, alone or with our collaboration partners, to successfully complete the development of, and obtain the regulatory approvals necessary to commercialize, our current and future product candidates. All of our product candidates are in the early stages of development. We do not anticipate generating revenues from product sales for at least the next several years, and we may never succeed in doing so. Our ability to generate future revenues from product sales depends heavily on our and our collaborators' and licensors' success in: ● completing preclinical and clinical development of our product candidates or product candidates incorporating our licensed capsids or other technologies and identifying new product candidates; ~~51~~ ● seeking and obtaining regulatory and marketing approvals for product candidates for which we or they complete clinical ~~trials~~ **development** ; ● launching and commercializing product candidates for which we or they obtain regulatory and marketing approval by establishing a sales, marketing and distribution infrastructure or, alternatively, collaborating with a commercialization partner; ● obtaining and maintaining adequate coverage and reimbursement by government and third- party payors for our product candidates if and when approved; ● maintaining and enhancing a sustainable, scalable, reproducible and transferable manufacturing process for our vectors and product candidates; ● establishing and maintaining supply and manufacturing relationships with third parties that have the financial, operating and technical capabilities to provide adequate products and services, in both amount and quality, to support clinical development and the market demand for our or their product candidates, if and when approved; ● obtaining an adequate level of market acceptance of our or their product candidates as ~~a~~ viable treatment ~~option~~ **options** ; ● addressing any competing technological and market developments; ● implementing additional internal systems and infrastructure, as needed; ● negotiating favorable terms in any collaboration, option, licensing, or other arrangements into which we may enter and performing our obligations in such collaborations; **52** ● obtaining, maintaining, protecting, enforcing and expanding our portfolio of intellectual property rights, including patents, trade secrets and know- how; ● avoiding and defending against third- party claims of interference or infringement; and ● attracting, hiring and retaining qualified personnel. Even if one or more of the product candidates that we develop is approved for commercial sale, we anticipate incurring significant costs associated with commercializing any approved product candidate. Our expenses could increase beyond expectations if we are required by the FDA, EMA, or other regulatory authorities to redesign or modify preclinical studies or clinical trials or to perform preclinical studies or clinical trials in addition to those that we currently anticipate. Even if we are able to generate revenues from the sale of any approved products, we may not become profitable and may need to obtain additional funding to continue operations. We will need to raise additional funding, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate certain of our product development efforts or other operations. We expect our expenses to increase over time in connection with our ongoing and planned activities, particularly as we continue the research and development of, continue or initiate clinical trials of, and seek marketing approval for, our product candidates. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant expenses related to product sales, medical affairs, marketing, manufacturing and distribution. We also continue to incur costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital or enter into business development transactions when needed or on acceptable terms, we could be forced to delay, reduce or eliminate certain of our research and development programs or any future commercialization efforts. ~~52Our~~ -- **Our** operations have consumed significant amounts of cash since inception. As of December 31, ~~2023~~ **2024** , our cash, cash equivalents, and marketable securities were $ ~~230~~ **332** . ~~9~~ **4** million. Based upon our current operating plan, we expect that our existing cash, cash equivalents, and marketable securities as December 31, ~~2023, together with the $ 80. 0 million upfront payment received in January~~ 2024 ~~in connection with the 2023 Novartis Collaboration Agreement, the $ 20. 0 million in proceeds from Novartis' stock purchase, and the $ 93. 5 million in net proceeds received from our public offering in January 2024,~~ along with amounts expected to be received as reimbursement for development costs under our collaboration and license agreements with Neurocrine and Novartis, ~~certain near- term milestones,~~ and interest income, to be sufficient to meet our planned operating expenses and capital expenditure requirements into **mid-** 2027. Our future capital requirements will depend on many factors, including: ● the scope, progress, results, and costs of product discovery, preclinical studies and clinical trials for our product candidates; **including our clinical trials to evaluate VY7523;** ● the scope, progress, results, costs, prioritization, and number of our research and development programs; ● the progress and status of our strategic collaborations and option and license agreements and any similar ~~arrangement~~ **arrangements** we may enter into in the future, including any research and development costs for which we are responsible, **future additional obligations that we may be committed to in connection with these agreements,** and our receipt of any **expense reimbursements,** future milestone payments and royalties from our collaboration partners or licensors; ● the extent to

which we are obligated to reimburse preclinical development and clinical trial costs, or the achievement of milestones or occurrence of other developments that trigger milestone and royalty payments, under any collaboration or license agreements to which we might become a party, such as ~~our~~ **the** license agreement **we entered into** with Touchlight IP Limited, or Touchlight **, in November 2022** , which we refer to as the Touchlight License Agreement; ● the costs, timing and outcome of regulatory review of our product candidates; **53** ● our ability to establish and maintain collaboration, distribution, or other marketing arrangements for our product candidates on favorable terms, if at all; ● the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property- related claims; ● the extent to which we acquire or in- license other product candidates and technologies, including any intellectual property associated with such candidates or technologies, acquire or invest in other businesses, or out- license our product candidates, capsids or other technologies; ● the costs of advancing our manufacturing capabilities and securing manufacturing arrangements for pre- commercial and commercial production; ● the level of product sales by us or our collaborators from any product candidates for which we obtain marketing approval in the future; ● the costs of operating as a public company and maintaining adequate product, clinical trial, and directors' and officers' liability insurance coverage; and ● the costs of establishing or contracting for sales, manufacturing, marketing, distribution, and other commercialization capabilities if we obtain regulatory approvals to market our product candidates. Identifying potential product candidates and conducting preclinical studies and clinical trials is a time- consuming, expensive, and uncertain process that takes years to complete. We may never generate the necessary data or results required to maintain the financial support of our collaborators or obtain marketing approval and achieve product ~~53sales~~ -- **sales** . In the event we are unable to achieve milestones necessary to demonstrate progress on those programs, a current or future collaboration partner or licensor may be unwilling to fund these programs at the desired levels or at all, which could require us to fund these programs to a greater extent than we have expected, to decline to pursue certain program objectives or to discontinue one or more of the programs. Our ability to develop a product candidate for any of our lead gene therapy or other biological therapy programs may take longer than we anticipate, or may not happen at all, and could require funding at a level higher than we expect. **In addition, our product candidates, if approved, may not achieve commercial success.** Our product revenues, if any, and any commercial milestone payments or royalty payments under our collaboration or option and license agreements **,** will be derived from sales of products that may not be commercially available for many years, if at all. ~~In addition, our product candidates, if approved, may not achieve commercial success.~~ Accordingly, we will need to continue to rely on additional financing and business development **transactions** to achieve our business objectives. Adequate additional financing ~~or business development transactions~~ may not be available to us on acceptable terms, or at all. ~~Raising~~ **54Raising** additional capital may cause dilution to our stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates. Until such time, if ever, as we can generate product revenues sufficient to achieve consistent profitability, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances, and option and license arrangements. We do not have any committed external source of funds other than the amounts we are entitled to receive from our collaboration partners **,** Neurocrine and Novartis **, and licensees** for the reimbursement of certain research and development expenses **, potential option exercises** , the achievement of specified regulatory and commercial milestones, and royalty payments under the 2019 Neurocrine Collaboration Agreement, the 2023 Neurocrine Collaboration Agreement, and the 2023 Novartis Collaboration Agreement and the amounts we are entitled to receive from our licensees Alexion and Novartis for the achievement of specified development, regulatory, and commercialization milestones and royalty payments under the applicable option and license agreements. To the extent that we raise additional capital through the sale of equity or equity- linked securities, including convertible debt, our stockholders' ownership interests will be diluted. The amount of stockholder dilution will be affected by the size of each securities offering and the offering price for the securities sold. The offering price will likely reflect the prevailing market price for our securities, with dilution increasing as the prevailing market price for our securities decreases. The terms of these securities may include liquidation or other preferences that adversely affect our existing stockholders' rights as holders of our common stock ~~. For example, we completed a private placement of 2, 145, 002 shares of our common stock to Novartis and an underwritten public offering of 7, 777, 778 shares of our common stock and pre- funded warrants to purchase up to 3, 333, 333 shares of our common stock in January 2024~~ . 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, obtaining additional capital, acquiring or divesting businesses, making capital expenditures or declaring dividends. 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. Our issuance of additional securities, whether equity or debt, or the possibility of such issuance, may cause the market price of our common stock to decline. Further, our existing stockholders may not agree with the terms of such financings. If we raise additional funds through collaborations, strategic alliances, or option and license arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or to grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market products or product candidates that we would otherwise prefer to develop and market ourselves. Such collaborations, alliances, or option and license arrangements could therefore cause the market price of common stock to decline. The early stage of our development efforts may make it difficult for our stockholders to evaluate the success of our business to date and to assess our future viability. Our operating history to date has been limited to building our team, business planning, raising capital, establishing our intellectual property portfolio, determining which neurological diseases to pursue, advancing our product candidates including delivery and manufacturing and conducting preclinical studies and early- phase clinical trials. Consequently, any predictions about our future success or viability may not be as accurate as they could be if we ~~54had~~ -- **had**

an operating history that included the late stage of clinical development, completion of clinical development, or commercialization of one or more product candidates. ~~All of~~ **VY7523,** our **anti- tau antibody candidate, is in early- stage clinical trials, and. all of our other** active product candidates are currently in preclinical development. In addition, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors such as the regulatory setbacks that previously occurred in prior clinical programs **, we have conducted** such as those put on hold by the FDA. These and other events that are part of our operating history may impact our ability to operate our business and to raise capital. All of our product candidates are in the early stages of development. To achieve our current goals, we will need to transition in the future from a company with a research and development focus to a company capable of supporting commercial activities. We may not be successful in such a transition. We expect our financial condition and operating results to continue to fluctuate significantly from quarter- to- quarter and year- to- year due to a variety of factors, many of which are beyond our control as we advance our programs ~~into~~ **55into** the clinical stage. Accordingly, our stockholders should not rely upon the results of any quarterly or annual periods as indications of future operating performance. Risks Related to the Development and Regulatory Approval of Our Product Candidates Our AAV gene therapy **, non- viral therapeutic,** and other biological therapy product candidates are based on a proprietary technology and, in several disease areas, unvalidated treatment approaches, which makes it difficult and potentially infeasible to predict the duration and cost of development of, and subsequently obtaining regulatory approval for, our product candidates. Our future success depends on our successful development of AAV gene therapy and other biological therapy product candidates, including our anti- tau antibody candidate **and non- viral therapeutic product candidates. VY7523, our anti- tau antibody candidate, is in early- stage clinical trials** . Each of the **other** product candidates we are advancing, either alone or together with our strategic collaborators, is currently in preclinical development. AAV gene therapies are a relatively new technology. We cannot accurately predict when or if any of our product candidates will prove effective or safe in humans or whether these product candidates will receive marketing approval. Additionally, there can be no assurance that we will not experience problems or delays in the preclinical testing or development of our product candidates and that such problems or delays will not cause unanticipated costs, or that any such problems or delays can be solved in a timely or profitable basis, if at all **. For example, we are no longer advancing VY9323, formerly the lead development candidate for our superoxide dismutase 1, or SOD1, silencing program for amyotrophic lateral sclerosis, or ALS, as a development candidate and are assessing alternate payloads for the program based on three- month data from a non- human primate good laboratory practice, or GLP, toxicology study suggesting that a different payload would be necessary to achieve the desired product profile for the program** . We also may experience unanticipated problems or delays in expanding our manufacturing capacity or outsourcing manufacturing activities to contract manufacturers. The clinical trial requirements of the FDA, the EMA and other regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty and intended use and market of the product candidate. The regulatory approval process for novel product candidates such as gene therapies can be more expensive and take longer than for other, better known or more extensively studied product candidates. Until August 2017, the FDA had never approved an AAV gene therapy product. Since that time, it has approved a limited number of gene therapy products. In Europe, a similarly limited number of AAV gene therapy products have been granted marketing authorization. It is difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in either the United States or the European Union or how long it will take to commercialize our product candidates. The few regulatory approvals of gene therapies to date may not be indicative of what the FDA, EMA, or other regulatory authorities may require for approval or whether different or additional preclinical studies or clinical trials may be required to support regulatory approval in a particular jurisdiction. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product 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. ~~55Regulatory~~ -- **Regulatory** requirements governing biological ~~and~~ **,** gene therapy **, and other non- viral therapeutic** products have changed frequently and may continue to change in the future. Such requirements may lengthen the regulatory review process, require us to modify current studies or perform additional studies or increase our development costs, which in turn may force us to delay, limit, or terminate certain of our programs. The Center for Biologics Evaluation and Research, or CBER, of the FDA regulates biological products, for human use. The Office of Tissues and Advanced Therapies, or OTAT, formerly known as the Office of Cellular, Tissue and Gene Therapies, within CBER reviews gene therapy and related products and has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER in its review. ~~U~~ **56U** . S. regulations require each clinical trial site' s institutional review board, or IRB, to review proposed clinical trials to assess the safety of the trial. If the protocol for such a trial was amended, it would need to be re- reviewed by the respective institutional IRBs of each institution. Any delay in or failure to obtain institutional IRB approval for any protocol or protocol amendment could delay, interrupt, or limit the conduct of the clinical trial at one or more participating clinical trial sites. Adverse or unforeseen developments in clinical trials of proprietary antibody and gene therapy products conducted by us or others may cause the FDA or other oversight bodies to change the requirements for approval of any of our product candidates. Similarly, EMA and local health authorities of individual countries within the European Union may issue new guidelines concerning the clinical development and marketing authorization for gene therapy medicinal products and require that we comply with these new guidelines. The EMA and agencies at both the federal and state level in the United States have expressed an interest in further regulating new biotechnologies, including gene therapy. In addition, gene therapy products are considered genetically- modified organism, or GMO, products and are regulated as such in each country. Designation of the type of GMO product and subsequent handling and disposal requirements can vary across countries and is variable throughout the European Union. Addressing each specific country requirement and obtaining approval to commence a clinical trial in these countries could result in delays in starting, conducting, or completing a clinical trial. Similar issues could be faced in other regions of the world ~~including the Asia- Pacific~~

~~region~~ . These regulatory review committees and advisory groups and the new guidelines they promulgate may lengthen the regulatory review process, require us to perform additional studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of these product candidates or lead to significant post- approval limitations or restrictions. As we advance our product candidates, we will be required to consult with these regulatory and advisory groups and comply with applicable guidelines. Any inability to receive timely, actionable feedback from regulatory authorities could also delay or otherwise hinder our development efforts. These and other regulatory delays may require us to incur additional clinical development costs, slow down our product candidate development and approval process and delay or potentially jeopardize our ability to commence product sales and generate revenue from our product candidates. We plan to continue to seek and incorporate FDA guidance in our ongoing development plans for each of our potential clinical candidates. If we fail to consult or solicit guidance from regulators or are unable to obtain sufficiently frequent or detailed guidance from regulators, we may be required to delay or discontinue development of certain of our product candidates. These additional processes may result in a review and approval process that is longer than we otherwise would have expected. Delays as a result of increased or lengthier regulatory approval process and further restrictions on development of our product candidates can be costly and could negatively impact our or our collaborators' ability to complete clinical trials and commercialize our current and future product candidates in a timely manner, if at all. Results from preclinical studies and early- stage clinical trials may not be indicative of efficacy in late- stage clinical trials. All of our product candidates are in early stages of development, and the risk of failure is high. Clinical testing is expensive, is difficult to design and implement, can take many years to complete and is uncertain as to outcome. A failure of one or more clinical trials can occur at any stage of testing. Our product candidates may fail to show the ~~56desired~~ -- **desired** safety and efficacy in preclinical testing or clinical development despite demonstrating promising results in earlier preclinical studies or clinical trials. In addition, the outcome of preclinical testing and early clinical trials may not be predictive of the success of later stage clinical trials. For example, despite data we believed was promising from the earlier PD- 1101 Phase 1b clinical trial and from the separate PD- 1102 Phase 1 clinical trial evaluating the delivery of VY- AADC (NBIb- 1817), we and our strategic collaborator Neurocrine did not receive favorable data, and were ultimately unable to complete, the RESTORE- 1 Phase 2 clinical trial evaluating VY- AADC (NBIb- 1817) for the treatment of Parkinson' s disease. Similarly, interim results generated from clinical trials do not necessarily predict final results, and results from one completed clinical trial may not be replicated in a subsequent clinical trial with a similar study design. Some of our clinical trials were conducted with small patient populations and were not blinded or placebo- controlled, making it difficult to predict whether the favorable results that we observed in such trials will be sustained or ~~repeated~~ **57repeated** in larger and more advanced clinical trials. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products. There is a high failure rate for product candidates proceeding through preclinical studies and clinical trials. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late- stage clinical trials even after achieving promising results in early- stage clinical trials. If a larger population of patients does not experience positive results, if these results are not reproducible, or if our products show diminishing activity over time, our products may not receive approval from the EMA or the FDA. Data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. In addition, we may encounter regulatory delays or rejections as a result of many factors, including changes in regulatory policy during the period of product development. Failure to confirm favorable results from earlier trials by demonstrating the safety and effectiveness of our products in late- stage clinical trials with larger patient populations could harm our business and we may never succeed in commercialization or generating product revenue. We **have conducted, and** may in the future conduct **,** clinical trials for product candidates at sites outside the United States, and the FDA may not accept data from trials conducted in such locations. **We have conducted, and may in the future choose to conduct, one or more of our clinical trials outside the United States.** To date, we have ~~only~~ conducted clinical trials in the United States **and Canada** . **We** ~~However, we~~ may in the future choose to conduct one or more of our clinical trials or include sites in current or future clinical trials outside the United States ~~. For example, we may include clinical trial sites outside the United States for our planned Phase 1 clinical trial to evaluate VY- TAU01~~ . Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of these data is subject to conditions imposed by the FDA. In cases where data from foreign clinical trials are intended to serve as the sole basis for marketing approval in the United States, the FDA will generally not approve the application on the basis of foreign data alone unless (i) the data are applicable to the U. S. population and U. S. medical practice; (ii) the trials were performed by clinical investigators of recognized competence and pursuant to GCP regulations; and (iii) the data may be considered valid without the need for an on- site inspection by the FDA, or if the FDA considers such inspection to be necessary, the FDA is able to validate the data through an on- site inspection or other appropriate means. In addition, even where the foreign trial data are not intended to serve as the sole basis for approval, the FDA will not accept the data as support for an application for marketing approval unless the trial satisfies certain conditions. For example, the clinical trial must be well- designed and conducted and performed by qualified investigators in accordance with ethical principles. The trial population must also adequately represent the U. S. population, and the data must be applicable to the U. S. population and U. S. medical practice in ways that the FDA deems clinically meaningful. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will depend on its determination that the trials also complied with all applicable U. S. laws and regulations. If the FDA does not accept the data from any trial we conduct outside the United States, it would likely result in the need for additional trials, which would be costly and time- consuming and would delay or permanently halt our development of the applicable product candidates. Even if the FDA accepted such data, it could require us to modify our planned clinical trials to receive clearance to initiate such trials in the United States or to continue such trials once initiated. ~~57Other~~ -- **Other** risks inherent in conducting international clinical trials or using international trial

sites include: ● foreign regulatory requirements **, differences in healthcare services, and differences in cultural customs** that could restrict or limit our ability to conduct our clinical trials; ● the administrative burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatment; ● the failure of enrolled patients to adhere to clinical protocols or inadequate collection and assessment of clinical data as a result of differences in healthcare services or cultural customs; **58** ● foreign exchange fluctuations; ● diminished or loss of protection of intellectual property in the relevant jurisdiction; and ● political, economic, environmental, and health risks relevant to specific foreign countries, including risks related to natural disasters or disease outbreaks. We are early in our development efforts. All of our active product candidates are currently in preclinical development or **early- stage** ~~are advancing into the clinic~~ **clinical development** . We may encounter substantial delays or difficulties in commencement, enrollment or completion of our preclinical studies or clinical trials, or we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities, any of which could prevent us from commercializing our current and future product candidates on a timely basis, if at all. We are early in our development efforts **. VY7523, our anti- tau antibody candidate, is currently in early- stage clinical trials** , and all of our **other** active product candidates are currently in preclinical development. Before obtaining marketing approval from regulatory authorities for the sale of our current and future product candidates, we must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidates. To conduct clinical trials, we must first complete preclinical testing and studies to support IND applications or similar applications in other jurisdictions. We cannot be certain of the timely completion or successful outcome of our preclinical testing and studies. Our ability to complete our preclinical testing and studies is contingent on, among other things, our ability to source animals and other supplies required for the conduct of such testing and studies. If we are unable to obtain such supplies, we may be unable to complete such preclinical testing and studies in a timely manner or at all. For example, some of our IND- enabling toxicology, capsid discovery, and other studies require certain ~~non- human primates, or~~ NHPs ~~,~~ that are customarily imported from outside the United States. Our inability to obtain access to a sufficient supply of these NHPs in a timely manner or at all may impair or delay our ability to complete preclinical studies to support capsid discovery efforts or IND applications or similar applications in other jurisdictions. We have previously encountered, and may encounter in the future, delays in obtaining a sufficient supply of such NHPs due to governmental or regulatory actions that result in importation restrictions in the United States or exportation restrictions in the country of origin. At times when the NHP supply in the United States has been constrained, we have conducted NHP studies at contract research facilities outside of the United States. When utilizing such facilities, we are required to observe export control regulations for the shipment of product candidates and their component materials and import control regulations for the shipment of samples to us for evaluation and storage. We may be required to incur delays or expenses in order to conduct our NHP studies in compliance with these regulations, and we may be subject to additional penalties, delays, or expenses if we fail to achieve compliance. Additionally, we cannot predict if the FDA or similar regulatory authorities outside the United States will accept our planned clinical programs or if the outcome of our preclinical testing and studies will ultimately support the further development of our preclinical and clinical programs. In connection with our VY- HTT01 Program for the treatment of Huntington' s disease, for example, we were unable to **successfully** predict what the FDA would require and were unable to obtain a second pre- IND meeting with the FDA to discuss the product candidate' s regulatory pathway with the FDA. As a result, in October 2020, the FDA notified us that the IND application for the planned Phase 1 and Phase 2 clinical trial to evaluate VY- HTT01 had been put on clinical hold. ~~58In~~ **In** addition, the FDA' s and other regulatory authorities' policies with respect to clinical trials may change and additional government regulations may be enacted. For example, in December 2022, with the passage of Food and Drug Omnibus Reform Act, known was FDORA, Congress required sponsors to develop and submit a diversity action plan **, or DAP,** for each Phase 3 clinical trial or any other " pivotal study " of a new drug or biological product. These plans are meant to encourage the enrollment of more diverse patient populations in late- stage clinical trials of FDA- regulated products. Specifically, action plans must include the sponsor' s goals for enrollment, the underlying rationale for those goals, and an explanation of how the sponsor intends to meet them. In addition to these requirements, the legislation directs the FDA to issue new guidance on **DAPs. In June 2024, as mandated by FDORA, the FDA issued draft guidance outlining the general requirements for DAPs. Unlike most guidance documents issued by the FDA, the DAP guidance when finalized will have the force of law because FDORA specifically dictates that the form and manner for submission 59of DAPs are specified in FDA guidance. On January 27, 2025, in response to an Executive Order issued by President Trump on January 21, 2025, on** ~~diversity~~ **Diversity , Equity and Inclusion programs, the FDA removed this draft guidance from its website. The implications of this** action ~~plans~~ **are not yet known** . Similarly, the regulatory landscape related to clinical trials in the European Union, or EU, recently evolved. The EU Clinical Trials Regulation, or CTR, which was adopted in April 2014 and repeals the EU Clinical Trials Directive, became applicable on January 31, 2022. While the Clinical Trials Directive required a separate clinical trial application, or CTA, to be submitted in each member state, to both the competent national health authority and an independent ethics committee, the CTR introduces a centralized process and only requires the submission of a single application to all member states concerned. The CTR allows sponsors to make a single submission to both the competent authority and an ethics committee in each member state, leading to a single decision per member state. The assessment procedure of the CTA has been harmonized as well, including a joint assessment by all member states concerned, and a separate assessment by each member state with respect to specific requirements related to its own territory, including ethics rules. Each member state' s decision is communicated to the sponsor via the centralized EU portal. Once the CTA is approved, clinical study development may proceed. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies governing clinical trials, our development plans may be impacted. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. A clinical trial failure can occur at any stage of testing. Similarly, there may be delays or difficulties in our initiation of future clinical trials. Similarly, there may be delays or difficulties in our initiation of future clinical trials. **For** ~~Due to the additional regulatory~~

~~uncertainties associated with gene therapy products, for~~ example, we ~~did not~~ **no** ~~initiate the RESTORE- 1 Phase 2~~ **longer expect to file an IND or Canadian** clinical trial **application** for ~~VY~~ **VY9323, formerly the lead development candidate for our SOD1 silencing program for ALS, and are assessing alternate payloads for the program based on three** ~~- AADC (NBIb~~ **month data from a non** ~~- 1817) as~~ **human primate GLP toxicology study suggesting that** a **different payload would be necessary** ~~treatment for Parkinson' s disease until we met with OTAT~~ to **achieve the desired product profile for the program** ~~discuss our proposed trial design and overall development plan~~ . We also have very limited historical experience with clinical trials **as a company** . Identifying and qualifying patients to participate in clinical trials of our product candidates is critical to our success. We may not be able to identify, recruit and enroll a sufficient number of patients, or those with required or desired characteristics, to complete our clinical trials in a timely manner or at all pursuant to the requirements of the FDA, EMA, or other regulatory authorities. Patient enrollment and trial completion are affected by many factors including: ● perceived risks and benefits of proprietary antibody ~~and~~ **,** AAV gene therapy **, and non- viral therapeutic** approaches for the treatment of neurological and other diseases; ● formulation changes to our product candidates, which may require us to conduct additional clinical studies to bridge our modified product candidates to earlier versions; ● size of the patient population and process for identifying patients; ● design of the trial protocol; ● eligibility and exclusion criteria; ● patients with preexisting antibodies to the gene therapy vector that preclude their participation in the trial; ● perceived risks and benefits of the product candidate under study; ● availability of competing therapies and clinical trials; ● severity of the disease under investigation; ~~59~~ ● availability of genetic testing for potential patients; **60** ● proximity and availability of clinical trial sites for prospective patients; ● lack of adequate compensation of patients; ● ability to obtain and maintain patient consent; ● risk that enrolled patients will drop out before completion of the trial; ● our ability to locate appropriately trained physicians to conduct such clinical trials, particularly for clinical trials requiring lengthy and highly complex surgical protocols, the performance of which may only be possible at major academic medical centers or specialized surgical centers; ● willingness of patients to participate in a placebo- controlled trial; ● patient referral practices of physicians; and ● ability to monitor patients adequately during and after treatment. Further, we plan to seek marketing approvals in the United States, **Canada,** the European Union and other jurisdictions, which may require that we conduct clinical trials in foreign countries. Our ability to successfully initiate, enroll and complete a clinical trial in any foreign country is subject to numerous risks unique to conducting business in foreign countries, including: ● difficulty in establishing or managing relationships with clinical research organizations, or CROs, and physicians; ● different standards for the conduct of clinical trials; ● absence in some countries of established groups with sufficient regulatory expertise for review of AAV gene therapy protocols; ● our inability to locate qualified local partners or collaborators for such clinical trials; and ● the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatment. If we have difficulty enrolling a sufficient number of patients to conduct our clinical trials as planned, we may need to delay, limit or terminate ongoing or planned clinical trials in some or all localities, any of which would harm our business, financial condition, results of operations and prospects. Other events that may prevent successful or timely completion of clinical development include: ● delays in reaching a consensus with regulatory authorities or collaborators on trial design, implementation, management, or other aspects of the clinical trial; ● delays in reaching agreement on acceptable terms with prospective CROs and clinical trial sites; ● delays in opening clinical trial sites or obtaining required IRB or independent ethics committee approval at each clinical trial site; ~~60~~ ● as a result of a serious adverse event, or SAE, or after an inspection of our clinical trial operations or trial sites or the decision by us or our collaborators, or the requirement of regulators or IRBs to suspend or ~~terminate~~ **61terminate** clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks; ● failure by us, our collaboration partners, any CROs we engage, or any other third parties to adhere to clinical trial protocols or regulatory requirements; ● failure by us, our collaboration partners, any CROs we engage, or any other third parties to perform in accordance with the FDA' s good clinical practices, or GCPs, or applicable regulatory guidelines in the European Union; ● failure by physicians to adhere to delivery protocols leading to variable results; ● delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites, including delays by third parties with whom we have contracted to perform certain of those functions; ● insufficient or inadequate supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates; ● 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 at a rate higher than we anticipate; ● selection of clinical endpoints that require prolonged periods of clinical observation or analysis of the resulting data; ● receipt of negative or inconclusive clinical trial results; ● occurrence of SAEs associated with the product candidate that are viewed to outweigh its potential benefits; ● occurrence of SAEs in trials of the same class of agents conducted by other sponsors; ● changes in regulatory requirements and guidance that require amending or submitting new clinical protocols; or ● the cost of clinical trials of our product candidates may be greater than we anticipate. Any inability to successfully initiate or complete preclinical studies and clinical trials could result in additional costs and potential delays to us or impair our ability to generate revenues from product sales, regulatory and commercialization milestones and royalties. We do not know whether any of our preclinical studies or clinical trials will begin as planned, will need to be restructured, or will be completed on schedule, or at all. For example, our decision to refocus our Huntington' s disease program means we must conduct new preclinical studies, prepare a new IND, submit it to the FDA, and resolve any potential FDA objections before enrolling our first patient in a new clinical trial. In addition, if we make manufacturing or formulation changes to our product candidates, such as our previous transition to an HEK 293- based production system from a baculovirus / Sf9 AAV production system or as a result of unanticipated clinical trial results, we may need to conduct additional studies to bridge our modified product candidates to earlier versions. Clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product

candidates and may harm our business, financial condition, results of operations and prospects. ~~61Additionally~~ **62Additionally** , if the results of our clinical trials are inconclusive or if there are safety concerns or SAEs associated with our product candidates, we may: ● be delayed in obtaining marketing approval for our product candidates, if we are able to do so 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 **or contraindications** ; ● 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 Risk Evaluation and Mitigation Strategy, or REMS ~~; ● be subject to the addition of labeling statements, such as warnings or contraindications~~ ; ● be sued or otherwise become party to dispute proceedings; or ● experience damage to our reputation. Our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit their commercial potential or result in significant negative consequences following any potential marketing approval. Our proprietary antibodies and gene therapy product candidates may cause an immunologic reaction, or an immune response against the relevant product candidate. Other potential side effects associated with our gene therapy product candidates could include insertional oncogenesis, which is the process whereby the insertion of a functional gene near a gene that is important in cell growth or division results in uncontrolled cell division, which could potentially enhance the risk of malignant transformation. In past clinical trials that were conducted by others using non- AAV gene therapy vectors, several significant side effects were caused by gene therapy treatments, including reported cases of leukemia and death. If our vectors demonstrate a similar adverse effect, or other adverse effects, we may be required to halt or delay further clinical development of our product candidates or withdraw the product from the market post- approval. For example, in a recently published review of patients with hepatocellular carcinomas, it was shown that a small subset contained an integrated genome sequence of wild- type AAV2 **,** and it was suggested that AAV2 may be associated with insertional oncogenesis. In addition to side effects caused by the product candidate, the administration process also could cause side effects. If in the future we are unable to demonstrate that such side effects were caused by the administration process or related procedures or are unable to modify the trial protocol adequately to address such side effects, the FDA, the European Commission, the EMA or other regulatory authorities could order us to cease further development of, or deny approval of, our product candidates for any or all targeted indications. For example, product candidates designed to " knock down " or reduce the expression of a gene or the production of its encoded protein ~~,~~ could have effects on other parts of the body, or " off target " effects, that could result in unforeseen toxicity. Even if we are able to demonstrate that any future SAEs are not product- related, and regulatory authorities do not order us to cease further development of our product candidates, such occurrences could affect patient recruitment or the ability of enrolled patients to complete the trial. Moreover, if we elect, or are required, to delay, suspend or terminate any clinical trial of any of our product candidates, the commercial prospects of such product candidates may be harmed and our ability to generate product revenues from any of these product candidates may be delayed or eliminated. Any of these occurrences may harm our ability to develop other product candidates and may harm our business, financial condition and prospects significantly. ~~62Additionally~~ **63Additionally** , if any of our product candidates receives marketing approval, the FDA could require us to adopt a REMS to ensure that the benefits outweigh its risks. We believe that the likelihood of the FDA requiring a REMS may be higher for treatments with more invasive routes of administration such as direct delivery through brain surgery. Such REMS may include, among other things, a medication guide outlining the risks of the product for distribution to patients and a communication plan to health care practitioners or the limitation of the use of the product to specifically trained neurosurgeons and / or certain centers. Furthermore, adverse events which were initially considered unrelated to the study treatment of the clinical trial may later be found to be caused by the study treatment. If we or others later identify undesirable side effects caused by our product candidate, several potentially significant negative consequences could result, including: ● regulatory authorities may suspend or withdraw approvals of such product candidate; ● regulatory authorities may require additional warnings on the label; ● we may be required to change the way a product candidate is administered or conduct additional clinical trials; ● we could be sued and held liable for harm caused to patients; and ● our reputation may suffer. Any of these events could prevent us from achieving or maintaining market acceptance of our product candidates and could significantly harm our business, prospects, financial condition and results of operations. We may be unable to obtain orphan drug designation or exclusivity for any of our product candidates for which we seek such designation. If our competitors are able to obtain orphan drug exclusivity for products that constitute the " same drug " and treat the same indications as our product candidates, we may not be able to have competing products approved by the applicable regulatory authority for a significant period of time. For products for which we may obtain orphan drug designation or exclusivity, we may be unable to prevent the approval or marketing authorization of other similar products based upon regulatory decisions regarding product " sameness ". Regulatory authorities in some jurisdictions, including the United States and the European Union, may designate drugs for relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, or the Orphan Drug Act, the FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as having a patient population of fewer than 200, 000 individuals 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 or biological product will be recovered from sales in the United States. In the European Union, EMA' s Committee for Orphan Medicinal Products grants orphan drug 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 not more than five in 10, 000 persons in the European Union. Additionally, orphan designation is granted for products intended for the diagnosis, prevention or treatment of a life- threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug or biologic product. Generally, if a product candidate with an orphan drug designation receives the first

marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the applicable regulatory authority from approving another marketing application for a product that constitutes the same drug treating the same indication for that marketing exclusivity period, except in limited circumstances. If another sponsor receives such approval before we do (regardless of our orphan drug designation), we may be precluded from receiving marketing approval for our product for the applicable exclusivity period. The applicable period is seven years in the United States and 10 years in the European Union. The exclusivity period in the United States can be extended by six months if the new drug application or BLA sponsor submits pediatric data that adequately respond to a written request from the FDA for such data. The exclusivity period in the European Union can be reduced to nine years if a ~~63product~~ **64product** no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be revoked if any regulatory agency determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition. We believe that certain of our current programs may qualify for orphan drug designation. Even if we obtain orphan drug exclusivity for a product candidate, that exclusivity may not effectively protect the product candidate from competition because different drugs or biological products can be approved for the same condition. In the United States, even after an orphan drug is approved, the FDA may subsequently approve another drug or biological product for the same condition if the FDA concludes that the other drug or biological product is not the " same drug " or biological product or even if it is, the FDA determines that it is clinically superior in that it is shown to be safer or more effective or makes a major contribution to patient care. In September 2021, the FDA issued final guidance describing its current thinking on when a gene therapy product is the " same " as another product for purposes of orphan exclusivity. Under the guidance, if either the transgene or vector differs between two gene therapy products in a manner that does not reflect " minor " differences, the two products would be considered different drugs for orphan drug exclusivity purposes. The FDA will determine whether two vectors from the same viral class are the same on a case- by- case basis and may consider additional key features in assessing the sameness. In the European Union, marketing authorization may be granted to a similar medicinal product for the same orphan indication if: ● the second applicant can establish in its application that its medicinal product, although similar to the orphan medicinal product already authorized, is safer, more effective or otherwise clinically superior; ● the holder of the marketing authorization for the original orphan medicinal product consents to a second orphan medicinal product application; or ● the holder of the marketing authorization for the original orphan medicinal product cannot supply sufficient quantities of orphan medicinal product. On August 3, 2017, the Congress passed the FDA Reauthorization Act of 2017, or FDARA. FDARA, among other things, codified the FDA' s pre- existing regulatory interpretation to require that a drug sponsor demonstrate the clinical superiority of an orphan drug that is otherwise the same as a previously approved drug for the same rare disease in order to receive orphan drug exclusivity. The new legislation reverses prior precedent holding that the Orphan Drug Act unambiguously requires that the FDA recognize the orphan exclusivity period regardless of a showing of clinical superiority. The FDA and Congress may further reevaluate the Orphan Drug Act and its regulations and policies, particularly in light of a decision from the U. S. Court of Appeals for the Eleventh Circuit ~~in~~ **. In** September 2021 ~~finding~~ **, the Court of Appeals for the 11th Circuit, in Catalyst Pharms, Inc. v. Becerra, or Catalyst, held** that, for the purpose of determining the scope of **orphan drug** exclusivity, the term " same disease or condition " **in the statute** means the designated " rare disease or condition " and could not be interpreted by the FDA to mean the " indication or use. " Thus, the ~~Court~~ **court** ~~of Appeals~~ concluded, orphan drug exclusivity applies to the entire designated disease or condition rather than the **approved** " indication or use. " **Although there have been legislative proposals to overrule this decision, they have not been enacted into law.** On January 23, 2023, the FDA announced that, in matters beyond the scope of ~~that~~ **the Catalyst** ~~Court~~ **court** ~~' s~~ order, the FDA will continue to apply its existing regulations tying orphan- drug exclusivity to the uses or indications for which the orphan drug ~~was~~ **is** approved. **More recently however** ~~We do not know if~~ , ~~when~~ **on February 14** , ~~or how~~ **2025, a federal district court in Washington, DC fully embraced** the **reasoning of** ~~FDA may change~~ the **Catalyst decision in another decision challenging the scope of** orphan drug ~~regulations and policies in the future~~ **exclusivity. The implications of this decision** , and ~~it~~ **its impact** ~~is uncertain how any changes might affect our business. Depending~~ on ~~what changes~~ the FDA ~~may make~~ **' s implementation of the Orphan Drug Act, are unclear at this point. In addition,** to ~~its~~ **obtain** orphan drug ~~regulations and policies~~ **designation in the European Union** , **we** ~~our business could~~ **would need to demonstrate that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized 65in the European Union or, if such method exists, the medicinal product will** be ~~adversely impacted~~ **of significant benefit to those affected by that condition** . ~~64A~~ **There is no assurance that we would be able to meet that standard for any of our product candidates. Further, if we do obtain orphan drug designation for a candidate product in the EU, we will not be able to maintain that designation if we are not able to show, to the satisfaction of the EU regulatory authorities, that the candidate product is of significant benefit to patients over available commercial products for the indication in the EU and any additional products that are ahead of our product candidate in clinical development for the indication. A** potential breakthrough therapy designation by the FDA for our product candidates may not lead to a faster development or regulatory review or approval process, and it does not increase the likelihood that our product candidates will receive marketing approval. We ~~have previously sought and~~ may in the future seek a breakthrough therapy designation for some of our product candidates. A breakthrough therapy is defined as a drug or biological product that is intended, alone or in combination with one or more other drugs, to treat a serious or life- threatening disease or condition, and preliminary clinical evidence indicates that the drug or biological 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. For drugs or biological products 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. Drugs designated as

breakthrough therapies by the FDA may also be eligible for accelerated approval. Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a breakthrough therapy designation for a product candidate may not result in a faster development process, review or approval compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that the drugs or biological products no longer meet the conditions for qualification. A potential regenerative medicine advanced therapy designation by the FDA for our product candidates may not lead to a faster development or regulatory review or approval process, and it does not increase the likelihood that our product candidates will receive marketing approval. We have sought and may in the future seek a regenerative medicine advanced therapy, or RMAT, designation for some of our product candidates. Under the 21st Century Cures Act, or the Cures Act, to be eligible to receive RMAT designation from the FDA, a product candidate must be (a) considered a " regenerative medicine therapy " as defined in the Cures Act; (b) intended to treat, modify, reverse, or cure one or more serious or life- threatening diseases or conditions; and (c) indicated, in preliminary clinical evidence, to have the potential to address unmet medical needs for such diseases or conditions. Gene therapies, including genetically modified cells, that lead to a durable modification of cells or tissues may meet the definition in the Cures Act of a regenerative medicine therapy. The RMAT program is intended to facilitate efficient development and expedite review of such therapies. A new drug application or a BLA for a product candidate that has received an RMAT designation may be eligible for priority review or accelerated approval through (1) surrogate or intermediate endpoints reasonably likely to predict long- term clinical benefit or (2) reliance upon data obtained from a meaningful number of sites. Benefits of such designation also include early interactions with FDA to discuss any potential surrogate or intermediate endpoint to be used to support accelerated approval. A product candidate that has received an RMAT designation that is granted accelerated approval and is subject to post- approval requirements may fulfill such requirements through the submission of clinical evidence, clinical studies, patient registries, or other sources of real world evidence, such as electronic health records; the collection of larger confirmatory data sets; or post- approval monitoring of all patients treated with such therapy prior to its approval. RMAT designation is within the discretion of the FDA. Accordingly, even if we believe one of our other product candidates meets the criteria for RMAT designation, the FDA may disagree and instead determine not to make ~~such~~ **66such** designation. In any event, the receipt of RMAT designation for a product candidate may not result in a faster development process, review or approval compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, the FDA may later decide that a product candidate that received RMAT designation no longer meets the conditions for designation. Alternatively, we or our collaborative partners may decide not to proceed with the clinical development of a product candidate that has previously received RMAT designation or decide to pursue such product candidate for an indication for which it has not received RMAT designation. ~~65Fast --~~ **Fast** Track designation by the FDA may not actually lead to a faster development or regulatory review or approval process and does not assure FDA approval of our product candidate. If a drug is intended for the treatment of a serious or life- threatening condition and the drug demonstrates the potential to address unmet medical need for this condition, the drug sponsor may apply for FDA Fast Track designation. We have sought and may in the future seek such a designation for our product candidates. A Fast Track designation does not ensure that the product candidate will receive marketing approval or that approval will be granted within any particular timeframe. Thus, Fast Track products may not experience a faster development process, review or approval compared to conventional FDA procedures. In addition, the FDA may withdraw Fast Track designation if it believes that the designation is no longer supported by data from a product candidate' s clinical development program. Fast Track designation alone does not guarantee qualification for the FDA' s priority review procedures. Priority review designation by the FDA may not lead to a faster regulatory review or approval process and, in any event, does not assure FDA approval of our product candidate. If the FDA determines that a product candidate offers major advances in treatment or provides a treatment where no adequate therapy exists, the FDA may designate the product candidate for priority review. A priority review designation means that the FDA' s goal to review an application is six months, rather than the standard review period of ten months. We may request priority review for our product candidates. The FDA has broad discretion with respect to whether or not to grant priority review status to a product candidate, so even if we believe a particular product candidate is eligible for such designation or status, the FDA may decide not to grant it. Moreover, a priority review designation does not necessarily mean a faster regulatory review process or necessarily confer any advantage with respect to approval compared to conventional FDA procedures. Receiving priority review from the FDA does not guarantee approval within the six- month review cycle or thereafter. **Where appropriate, we may pursue approval from the FDA, EMA or comparable foreign regulatory authorities through the use of accelerated registration 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 appropriate, we plan to pursue accelerated development strategies in areas of medical need. We may seek an accelerated approval pathway for one or more of our product 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 product candidate designed to treat a serious or life- threatening condition that provides meaningful therapeutic benefit over available therapies upon a determination that the product 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 67other clinical benefit. The accelerated approval pathway may be used in cases in which the advantage of a new drug or biologic 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 or biologic' s clinical benefit. If such post- approval studies fail to confirm the drug' s or biologic' s clinical benefit, the FDA may withdraw its approval of the product. In addition, there can be no assurance that we will satisfy all FDA requirements, including new provisions, that govern accelerated approval. For example, with passage of the FDORA in December 2022, Congress modified certain provisions governing accelerated approval of drug and biologic products. Specifically, the new legislation authorized the FDA to require a sponsor to have its confirmatory clinical trial underway before accelerated approval is awarded and to submit progress reports on its post- approval studies to FDA every six months until the study is completed. Moreover, FDORA established expedited procedures authorizing FDA to withdraw an accelerated approval if certain conditions are met, including where a required confirmatory study fails to verify and describe the predicted clinical benefit or where evidence demonstrates the product is not shown to be safe or effective under the conditions of use. The FDA may also use such procedures to withdraw an accelerated approval if a sponsor fails to conduct any required post- approval study of the product with due diligence, including with respect to " conditions specified by the Secretary. " The new procedures include the provision of due notice and an explanation for a proposed withdrawal, and opportunities for a meeting with the Commissioner or the Commissioner' s designee and a written appeal, among other things. We will need to fully comply with these and other requirements in connection with the development and approval of any product candidate that qualifies for accelerated approval. More recently, in March 2023, the FDA issued draft guidance that outlines its current thinking and approach to accelerated approval. The FDA indicated that the accelerated approval pathway is commonly used for approval of oncology drugs due to the serious and life- threatening nature of cancer. Although single- arm trials have been commonly used to support accelerated approval, a randomized controlled trial is the preferred approach as it provides a more robust efficacy and safety assessment and allows for direct comparisons to an available therapy. To that end, the FDA outlined considerations for designing, conducting, and analyzing data for trials intended to support accelerated approvals of oncology therapeutics. Subsequently, in December 2024 and January 2025, the FDA issued additional draft guidance relating to accelerated approval. This guidance describes FDA' s views on what it means to conduct a confirmatory trial with due diligence and how the agency plans to interpret whether such a study needs to be underway at the time of approval. While this guidance is currently only in draft form and will ultimately not be legally binding even when finalized, we will need to consider the FDA' s guidance if we seek accelerated approval for any of our products in the future. 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 a 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 submission or application will be accepted or that any expedited development, review or 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. A failure to obtain accelerated approval, review or approval for our product candidate would result in a longer time period to commercialization of such product candidate, could increase the cost of development of such product candidate and could harm our competitive position in the marketplace. 68Even** if we complete the necessary preclinical studies and clinical trials, the marketing approval process is expensive, time- consuming and uncertain and may prevent us from obtaining approvals for the commercialization of some or all of our product candidates. If we or any current or future collaborators are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we or they may not be able to commercialize our products, and our ability to generate revenue may be materially impaired. Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, export and import, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the EMA and comparable regulatory authorities in other countries. Failure to obtain marketing approval for a product candidate will prevent us from commercializing the product candidate. We have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction. We have only limited experience in filing and supporting the applications necessary to gain marketing approvals and expect to rely on third- party CROs to assist us in this process. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the product candidate' s safety and efficacy. Securing regulatory approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or

unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use. **Further, the FDA may determine that we must provide additional evidence and data before approving a BLA or NDA for our candidate products. For example, the FDA reviews an application to determine whether there is " substantial evidence " to support a finding of effectiveness for the proposed product for its intended use (s). The FDA has interpreted this evidentiary standard to generally require at least two adequate and well- controlled clinical trials to establish effectiveness of a new product. Under certain circumstances, however, the FDA has indicated that a single trial with certain characteristics and additional confirmatory evidence may satisfy this standard. The FDA issued draft guidance in September 2023 that outlines considerations for relying on confirmatory evidence in lieu of a second clinical trial to demonstrate effectiveness. In the event that we submit a BLA or NDA on the basis of one clinical trial and confirmatory evidence, the FDA could determine that such information is not sufficient to support approval of the application and the agency could require us to conduct an additional trial in support of the BLA or NDA.** The FDA may also require that NDA **or BLA** submissions for our product candidates include pediatric data. Under the PREA, an NDA, BLA or supplement to an NDA or BLA for certain drugs and biological products must contain data to assess the safety and effectiveness of the drug or biological product in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective, unless the sponsor receives a deferral or waiver from the FDA. Applicable legislation in the EU also requires sponsors to either conduct clinical trials in a pediatric population in accordance with a Pediatric Investigation Plan approved by the ~~66Pediatric~~ **Pediatric** Committee of the European Medicines Agency, or EMA, or to obtain a waiver or deferral from the conduct of these studies by this Committee. For any of our product candidates for which we are seeking regulatory approval in the United States or the EU, we cannot guarantee that we will be able to obtain a waiver or alternatively complete any required studies and other requirements in a timely manner, or at all, which could result in associated reputational harm and subject us to enforcement action **. Moreover, principal investigators for our future clinical trials may serve as scientific advisors or consultants to us and receive compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA or comparable foreign regulatory authorities. The FDA or a comparable foreign regulatory authority may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the study. The FDA or comparable foreign regulatory authority may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing 69applications by the FDA or comparable foreign regulatory authority, as the case may be, and may ultimately lead to the denial of marketing approval of one or more of our product candidates** . The process of obtaining marketing approvals, both in the United States and abroad, is expensive; may take many years if additional clinical trials are required, if approval is obtained at all and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. In the United States, for example, the application user fee to obtain FDA review of a marketing application is more than $ 4. ~~0~~ **3** million ~~,~~ and may be higher in the future. Changes in marketing approval policies during the development period, in or the enactment of additional statutes or regulations, or in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. The FDA and comparable authorities in other countries have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we, or any current or future collaborators, ultimately obtain may be limited or subject to restrictions or post- approval commitments that render the approved product not commercially viable. Accordingly, if we or any current or future collaborators experience delays in obtaining approval or if we or they fail to obtain or retain approval of our product candidates and devices, the commercial prospects for our product candidates may be harmed and our ability to generate revenues could be materially impaired. Even if we obtain regulatory approval for a product candidate, our products will remain subject to regulatory oversight. Even if we obtain any regulatory approval for our product candidates, they will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storing, advertising, promoting, sampling, record- keeping and submitting safety and other post- market information. Any regulatory approvals that we receive for our product candidates also may be subject to a REMS, limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval or contain requirements for potentially costly post- marketing testing, including post- marketing studies or clinical trials, and surveillance to monitor the quality, safety and efficacy of the product. 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. FDA guidance advises that patients treated with some types of gene therapy undergo follow- up observations for potential adverse events for as long as 15 years. The holder of an approved BLA also must submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws. In addition, product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with cGMP requirements and adherence to commitments made in the BLA or foreign marketing application. If we, or a regulatory authority, discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured or such regulatory authority disagrees with the promotion, marketing or labeling of that product, the regulatory authority may impose restrictions relative to that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing. If we fail to comply with applicable regulatory requirements following approval of any of our product candidates, a regulatory authority may: ● issue a warning letter asserting that we are in violation of the law;

● seek an injunction or impose administrative, civil or criminal penalties or monetary fines; ~~67~~ ● suspend or withdraw regulatory approval; **70** ● suspend any ongoing clinical trials; ● refuse to approve a pending BLA or comparable foreign marketing application, or any supplements thereto, submitted by us or our collaboration partners; ● restrict the marketing or manufacturing of the product; ● seize or detain the product or otherwise require the withdrawal of the product from the market; ● refuse to permit the import or export of products; 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 our product candidates and adversely affect our business, financial condition, results of operations and prospects. **In addition, we could be adversely affected by several significant administrative law cases decided by the U. S. Supreme Court in 2024. In Loper Bright Enterprises v. Raimondo, for example, the Court overruled Chevron U. S. A., Inc. v. Natural Resources Defense Council, Inc., which for 40 years required federal courts to defer to permissible agency interpretations of statutes that are silent or ambiguous on a particular topic. The U. S. Supreme Court stripped federal agencies of this presumptive deference and held that courts must exercise their independent judgment when deciding whether an agency such as the FDA acted within its statutory authority under the Administrative Procedure Act, or the APA. Additionally, in Corner Post, Inc. v. Board of Governors of the Federal Reserve System, the Court held that actions to challenge a federal regulation under the APA can be initiated within six years of the date of injury to the plaintiff, rather than the date the rule is finalized. The decision appears to give prospective plaintiffs a personal statute of limitations to challenge longstanding agency regulations. Another decision, Securities and Exchange Commission v. Jarkesy, overturned regulatory agencies' ability to impose civil penalties in administrative proceedings. These decisions could introduce additional uncertainty into the regulatory process and may result in additional legal challenges to actions taken by federal regulatory agencies, including the FDA and CMS, that we rely on. In addition to potential changes to regulations as a result of legal challenges, these decisions may result in increased regulatory uncertainty and delays and other impacts, any of which could adversely impact our business and operations.** Further, our ability to develop and market new drug products may be impacted by ~~ongoing~~ litigation challenging the FDA' s approval of ~~mifepristone~~ **another company' s drug product** . **In** ~~Specifically, on~~ April ~~7,~~ 2023, the U. S. District Court for the Northern District of Texas ~~stayed~~ **invalidated** the approval by the FDA of mifepristone, a drug product which was originally approved in 2000 and whose distribution is governed by various ~~conditions~~ **measures** adopted under a REMS. **The** ~~In reaching that decision, the District Court made a number of findings that may negatively impact the development, approval and distribution of drug products in the United States. Among other determinations, the District Court held that plaintiffs were likely to prevail in their claim that FDA had acted arbitrarily and capriciously in approving mifepristone without sufficiently considering evidence bearing on whether the drug was safe to use under the conditions identified in its labeling. Further, the District Court read the standing requirements governing litigation in federal court as permitting a plaintiff to bring a lawsuit against the FDA in connection with its decision to approve an NDA or establish requirements under a REMS based on a showing that the plaintiff or its members would be harmed to the extent that FDA' s drug approval decision effectively compelled the plaintiffs to provide care for patients suffering adverse events caused by a given drug. On April 12, 2023, the District Court decision was stayed, in part, by the U. S.~~ Court of Appeals for the Fifth Circuit ~~. Thereafter, on April 21, 2023, the U. S. Supreme Court entered a stay of the District Court' s decision, in its entirety, pending disposition of the appeal of the District Court decision in the Court of Appeals for the Fifth Circuit and the disposition of any petition for a writ of certiorari to or the U. S. Supreme Court. The Court of Appeals for the Fifth Circuit held oral argument in the case on May 17, 2023 and, on August 16, 2023, issued its decision. The Court of Appeals~~ declined to order the removal of mifepristone from the market **but** ~~, finding that a challenge to the FDA' s initial approval in 2000 is barred by the statute of limitations. But the Court of Appeals~~ did hold that plaintiffs were likely to prevail in their claim that changes allowing for expanded access of mifepristone ~~that~~ **, which the** FDA authorized in 2016 and 2021 **,** were arbitrary and capricious. **In June** ~~On September 8, 2023~~ **2024** , the ~~Justice Department and a manufacturer of mifepristone filed petitions for a writ of certiorari, requesting that asked the United States~~ Supreme Court **reversed that** ~~to review the Court of Appeals~~ decision **after unanimously finding that the plaintiffs (anti- abortion doctors and organizations) did not have standing to bring this legal action against the FDA** . On ~~December 13~~ **October 11** , ~~2023~~ **2024** , **the Attorneys General of** ~~the~~ **three** ~~U. S. Supreme~~ **states (Missouri, Idaho and Kansas) filed an amended complaint in the district** ~~Court~~ **court** ~~granted~~ **in Texas challenging FDA' s actions. On January 16, 2025, the district court agreed to allow** these ~~petitions~~ **states to file an amended complaint and continue to pursue this challenge. Depending on the outcome of this litigation, our ability to develop new drug product candidates and to maintain approval of existing drug products could be delayed, undermined** ~~for~~ **or subject to protracted litigation** ~~writ of certiorari for the appeals court decision~~ . In addition, FDA policies, and those of equivalent foreign regulatory agencies, may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, ~~we~~ **71we** may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would harm our business, financial condition, results of operations and prospects. ~~68~~**We Disruptions in the FDA and other government agencies caused by funding shortages or global health concerns could hinder their ability to hire and retain key leadership and other personnel or otherwise prevent new product candidates and services from being developed or commercialized in a timely manner, which could negatively impact our business. The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes 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, including those that fund research and development activities, is subject to the political process, which is inherently fluid and unpredictable. Disruptions at the FDA and other agencies may also slow the time necessary for new product candidates to be reviewed or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including for 35 days beginning on December 22, 2018, the U. S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. In addition, disruptions may result from events similar to the COVID- 19 pandemic. 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. In the event of a similar public health emergency in the future, the FDA may not be able to continue its current pace and review timelines could be extended. Regulatory authorities outside the United States facing similar circumstances may adopt similar restrictions or other policy measures in response to a similar public health emergency and may also experience delays in their regulatory activities. Further, with the change in presidential administrations in 2025, there is substantial uncertainty as to how, if at all, the new administration will seek to modify or revise the requirements and policies of the FDA and other regulatory agencies with jurisdiction over our product candidates. There is also uncertainty as to how other measures being implemented by the Trump Administration across the government will impact our activities and those of the FDA and its operations. For example, the potential loss of FDA personnel could lead to further disruptions and delays in FDA review of our product candidates and FDA guidance regarding our or our collaborators' clinical development programs. Similarly, efforts by the new administration to substantially reduce research funding by the National Institutes of Health of medical research could have substantial direct or indirect impacts on our research activities. Accordingly, if a prolonged government shutdown or other disruption occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Future shutdowns or other disruptions could also affect other government agencies such as the SEC, which may also impact our business by delaying review of our public filings, to the extent such review is necessary, and our ability to access the public markets. We** face significant competition in an environment of rapid technological change and the possibility that our competitors may achieve regulatory approval before us or develop therapies that are more advanced or effective than ours, which may harm our business and financial condition and our ability to successfully market or commercialize our product candidates. The biopharmaceutical industry is characterized by intense and dynamic competition to develop new technologies and proprietary therapies. Any product candidates that we successfully develop into products and commercialize may compete with existing therapies and new therapies that may become available in the future. While we believe that our gene therapy platform, vectorized antibody platform, **non- viral therapeutics platform,** product programs, product candidates and scientific expertise in the fields of proprietary antibodies, gene therapy, and ~~neuroscience~~ **72neuroscience** provide us with competitive advantages, we face potential competition from various sources, including larger and better- funded pharmaceutical, specialty pharmaceutical and biotechnology companies, as well as from academic institutions, governmental agencies and public and private research institutions. We are aware of several companies focused on developing their proprietary antibodies ~~or ,~~ AAV gene therapies **, or non- viral therapeutics** in various indications, as well as several companies addressing other methods for modifying genes and regulating gene expression. Any advances in antibody ~~or ,~~ gene therapy **, or non- viral therapeutic** technology made by a competitor may be used to develop therapies that could compete against any of our product candidates. We expect that our TRACER discovery platform **, non- viral therapeutics platform, and clinical** and preclinical programs will compete with a variety of therapies in development, including: ● Our anti- tau antibody and tau silencing gene therapy programs for AD will potentially compete with tau antibodies being developed by Lundbeck **LLC** ~~Inc.~~, Merck & Co. **,** Inc. in collaboration with Teijin Limited, ~~Roche Genentech Inc. in collaboration with AC Immune SA,~~ Eisai Co., Ltd., Janssen Pharmaceuticals, Inc., UCB S. A., Bristol **-** Myers Squibb Company in collaboration with ~~Prothera~~ **Prothena** ~~Inc.~~ **Corporation plc** , along with several other companies, as well as an antisense oligonucleotide program being developed by Ionis in collaboration with Biogen; ● Our program for a monogenic form of ALS will potentially compete with ~~Tofersen~~ **tofersen** being developed by Biogen, in collaboration with Ionis, and gene therapies being developed by Novartis Gene Therapies, Inc. and uniQure, Inc.; and ● Our TRACER discovery platform will potentially compete with a variety of companies developing AAV capsids, including: 4D Molecular Therapeutics, Inc., Affinia Therapeutics Inc., Apertura Gene Therapy, LLC, Capsida Biotherapeutics, Inc., Capsigen, Inc., Dyno Therapeutics, Inc., Kate Therapeutics, Inc., **Sangamo Therapeutics, Inc.,** and Shape Therapeutics **Inc. ● Our non- viral therapeutics platform will potential compete with a variety of companies developing non- viral shuttles for the delivery of genetic medicines to the CNS, including: ABL Bio, Inc. in collaboration with Sanofi S. A., Aliada Therapeutics, Inc. (acquired by AbbVie Inc.), Arrowhead Pharmaceuticals, Inc. in collaboration with Sarepta Therapeutics, Inc., BioArctic AB in collaboration with Eisai Co., Ltd., Denali Therapeutics Inc., F. Hoffmann- La Roche Ltd JCR Pharmaceuticals Co., Ltd., and Souffle Therapeutics,** Inc. Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical and other resources, such as larger research and development, clinical, marketing and manufacturing organizations. Mergers and acquisitions in the biotechnology and pharmaceutical industries, including recent transactions involving a number of gene therapy companies, may result in even more resources being concentrated among a smaller number of competitors. Smaller and other early- stage companies may also prove to be significant competitors, particularly through collaborative agreements with large and established companies. Our commercial opportunity could be reduced or eliminated if competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any

products that we may develop. **Even if our competitors are unsuccessful in developing and commercializing their product candidates, their preclinical and clinical findings may lead us to conclude that our own similar product candidates are unlikely to achieve the desired performance characteristics. As a result, we may modify our development plans for, or discontinue further research and development of, such product candidates. For example, several of our competitors are conducting clinical trials of anti- tau antisense oligonucleotide and antibody candidates with expected clinical data readouts in 2025 and 2026. It is possible that we will modify our development plans for, or discontinue further research and development of, VY7523 or VY1706, the lead development candidate for our tau gene silencing gene therapy program, if any of these clinical data readouts suggest that either candidate will likely fail to achieve the desired performance characteristics.** ~~Competitors~~ **73Competitors** also may obtain FDA or other regulatory approval for their products more rapidly or earlier than us or may obtain orphan drug or other marketing exclusivity, which could result in our competitors establishing a strong market position before we are able to enter the market or reducing the number of available subjects for enrollment in our clinical trials to support regulatory submissions and approvals of our product. Additionally, technologies developed or acquired by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors. These third parties also compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites, and registering patients for clinical trials. ~~69In~~ **In** addition, as a result of the expiration or successful challenge of our patent rights, we could face more litigation with respect to the validity and scope of patents relating to our competitors' products. The availability of our competitors' products could limit the demand, and the price we are able to charge, for any products that we may develop and commercialize. If we are not able to compete effectively against potential competitors, our business will not grow, and our financial condition and operations will be harmed. Even if we obtain and maintain approval for our product candidates from the FDA, we may never obtain approval for our product candidates outside of the United States, which would limit our market opportunities and adversely affect our business. Approval of a product candidate in the United States by the FDA does not ensure approval of such product candidate by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA. Sales of our product candidates outside of the United States will be subject to foreign regulatory requirements governing clinical trials and marketing approval. Even if the FDA grants marketing approval for a product candidate, comparable regulatory authorities of foreign countries also must approve the manufacturing and marketing of the product candidates in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and more onerous than, those in the United States, including additional preclinical studies or clinical trials or manufacturing control requirements. In many countries outside the United States, a product candidate must be separately approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for our products, if approved, is also subject to approval. We intend to submit a marketing authorization application to EMA for approval of our product candidates in the European Union but obtaining such approval from the European Commission following the opinion of EMA is a lengthy and expensive process. Even if a product candidate is approved, the FDA or the European Commission may limit the indications for which the product may be marketed, require extensive warnings on the product labeling or require expensive and time- consuming additional clinical trials or reporting as conditions of approval. Regulatory authorities in countries outside of the United States and the European Union also have requirements for approval of product candidates with which we must comply prior to marketing in those countries. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our product candidates in certain countries. Further, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries. Regulatory approval for any of our product candidates may be withdrawn. If we fail to comply with the regulatory requirements, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed and our business, financial condition, results of operations and prospects will be harmed. ~~Further~~ **Additionally**, we could face heightened risks with respect to obtaining marketing authorization in the UK as a result of the withdrawal of the UK from the EU, commonly referred to as Brexit. The UK is no longer part of the European Single Market and EU Customs Union. As of January 1, ~~2021~~ **2025**, the Medicines and Healthcare ~~products~~ **Products** Regulatory Agency, or ~~the~~ MHRA, ~~became responsible for supervising medicines and medical devices in Great Britain, comprised of England, Scotland and Wales under domestic law, whereas under the terms of the Northern Ireland Protocol, Northern Ireland~~ is ~~currently subject to EU rules. The UK and EU have however agreed to the Windsor Framework which fundamentally changes the existing system under the Northern Ireland Protocol, including with respect to the regulation of medicinal products in the UK. Once implemented, the changes introduced by the Windsor Framework will see the MHRA be~~ responsible for approving all medicinal products destined for the ~~entire UK~~ **United Kingdom** market (i. e., ~~both~~ Great Britain and Northern Ireland) **. At the same time**, **a new international recognition procedure, or IRP, will apply, which intends to facilitate approval of pharmaceutical products in the UK. The IRP is open to applicants that have already received** ~~and~~ **an authorization for** the **same product from one of the MHRA' s specified Reference Regulators, or RRs. The RRs notably include** EMA **and regulators in the EU / European Economic Area member states for approvals in 74the EU centralized procedure and mutual recognition procedure as** ~~will~~ **well** ~~no longer have~~ **as the FDA (for product approvals granted in the United States). However, the concrete functioning of the IRP is currently unclear. Any delay in obtaining, or an inability to obtain,** any ~~role~~ **marketing approvals may force us or our collaborators to restrict or delay efforts to seek regulatory approval** in ~~approving medicinal~~ **the UK for our** ~~products~~ **product** ~~destined for Northern Ireland~~ **candidates, which could significantly and materially harm our business**. In addition, foreign regulatory authorities may change their approval policies and new regulations may be enacted. For instance, the EU pharmaceutical legislation is currently undergoing a complete review process, in the context of the Pharmaceutical Strategy for Europe initiative, launched by the European Commission in November 2020. The European

Commission' s proposal for revision of several legislative instruments related to medicinal products ( **including** potentially reducing the duration of regulatory data protection ~~,~~ **and** revising the eligibility for expedited pathways ~~, etc.~~ ) was ~~70published~~ -- **published** on April 26, 2023. The proposed revisions remain to be agreed and adopted by the European Parliament and European Council and the proposals may therefore be substantially revised before adoption, which is not anticipated before early 2026. The revisions may however have a significant impact on the pharmaceutical industry and our business in the long term. We expect that we will be subject to additional risks in commercializing any of our product candidates that receive marketing approval outside the United States, including tariffs, trade barriers and regulatory requirements; economic weakness, including inflation, increasing interest rates, or political instability in particular foreign economies and markets; compliance with tax, employment, immigration and labor laws for employees living or traveling abroad; foreign currency fluctuations, which could result in increased operating expenses and reduced revenue, and other obligations incident to doing business in another country; and workforce uncertainty in countries where labor unrest is more common than in the United States. If approved, our product candidates that are licensed and regulated as biologics may face competition from biosimilars approved through an abbreviated regulatory pathway. The Biologics Price Competition and Innovation Act of 2009, or BPCIA, was enacted as part of the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively, the ACA, to establish an abbreviated pathway for the approval of biosimilar and interchangeable biological products. The regulatory pathway establishes legal authority for the FDA to review and approve biosimilar biologics, including the possible designation of a biosimilar as " interchangeable " based on its similarity to an approved biologic. Under the BPCIA, a reference biological product is granted 12 years of data exclusivity from the time of first licensure of the product, and the FDA will not accept an application for a biosimilar or interchangeable product based on the reference biological product until four years after the date of first licensure of the reference product **.** In addition, the licensure of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first licensed. During this 12- year period of exclusivity, another company may still develop and receive approval of a competing biologic, so long as its BLA does not rely on the reference product or sponsor' s data, or the company does not submit the application as a biosimilar application. We believe that any of the product candidates we develop as a biological product under a BLA should qualify for the 12- year period of exclusivity. However, there is a risk that this exclusivity could be shortened due to congressional action or otherwise, or that the FDA will not consider the subject product candidates to be reference products for competing products, potentially creating the opportunity for biosimilar competition sooner than anticipated. Moreover, the extent to which a biosimilar, once approved, will be substituted for any one of the reference products in a way that is similar to traditional generic substitution for non- biological products will depend on a number of marketplace and regulatory factors that are still developing. Nonetheless, the approval of a biosimilar to our product candidates would have a material adverse impact on our business due to increased competition and pricing pressure. ~~Risks~~ **75Risks** Related to Third PartiesTo date, **substantially** all of our revenue has been derived from our ongoing collaborations and licensing agreements with Neurocrine, Novartis, **and** Alexion ~~, and Sangamo Therapeutics, Inc., or Sangamo~~ , and from our prior collaborations with Sanofi Genzyme, AbbVie Biotechnology Ltd and AbbVie Ireland Unlimited Company, or AbbVie. If any ongoing or future collaboration, option and license, or license agreements were to be terminated, our business financial condition, results of operations and prospects could be harmed. To date, **substantially** all of our revenue has been derived from our ongoing collaborations and licensing agreements with Neurocrine, Novartis, **and** Alexion ~~and Sangamo~~ and from our prior collaborations with Sanofi Genzyme ~~Corporation~~ , AbbVie Biotechnology Ltd and AbbVie Ireland Unlimited Company. If any ongoing or future collaboration, option and license, or license agreements were to be terminated, our business financial condition, results of operations and prospects could be harmed. **Our ability to generate revenues from** ~~For example, certain of our prior collaborations were terminated. As a result of the~~ **these arrangements will depend** ~~terminations of our collaborations with Sanofi Genzyme and AbbVie, we ceased to be eligible to receive option and milestone payments pursuant to the collaborations or to receive royalties in connection with any potential products developed under the collaborations. 71On February 2, 2021, Neurocrine notified us that it had elected to terminate the 2019 Neurocrine Collaboration Agreement solely with regards to the VY- AADC Program. This termination became effective August 2, 2021, which we refer to as the Neurocrine VY- AADC Program Termination Effective Date. The 2019 Neurocrine Collaboration Agreement remains in full force and effect for each other program thereunder. Upon the termination of the VY- AADC Program, the license granted by us to Neurocrine regarding the VY- AADC Program expired, and we regained worldwide intellectual property rights to the VY- AADC Program in accordance with the collaboration agreement, and the restrictions~~ on ~~us to develop, manufacture or~~ **our** ~~commercialize a gene therapy product directed to the targets specified in the VY- AADC Program terminated. If Neurocrine were to terminate the remainder of the 2019 Neurocrine Collaboration~~ **collaborators** ~~Agreement, we would become responsible for all research and development expenses relating to the remaining Neurocrine Programs and would not receive any future milestone payments or royalty payments under the 2019 Neurocrine Collaboration Agreement with respect to such programs. In October 2021, we entered into an option and license agreement with Pfizer, or the Pfizer Agreement, pursuant to which we granted Pfizer options to receive an exclusive license, or the Pfizer License Options, to certain novel capsids we have generated using our TRACER Capsid discovery platform, or TRACER Capsids, to develop and commercialize certain AAV gene therapy candidates comprised of a capsid and specified Pfizer transgenes, or Pfizer Transgenes. Effective as of September 30, 2022, Pfizer exercised a Pfizer License Option with respect to a capsid for the specified Pfizer Transgene for potential treatment of a rare neurological disease. In connection with the exercise of the Pfizer License Option for a rare neurological disease, we granted Pfizer an exclusive, worldwide license, with the right to sublicense, under certain of our intellectual property, the rights to develop and commercialize rare neurological disease products utilizing the capsid candidate and incorporating the corresponding Pfizer Transgene, or the Pfizer Licensed CNS Products. Pfizer did not exercise its option to license a capsid for the potential treatment of a cardiovascular disease. As result, Pfizer~~ ' ~~s right to exercise a Pfizer License Option for a cardiovascular disease has terminated in accordance with the terms of the Pfizer~~

~~Agreement and all rights to capsids for that cardiovascular disease have reverted to us. On July 28, 2023, Alexion, AstraZeneca Rare Disease, or Alexion, entered into a definitive purchase and license agreement for preclinical gene therapy assets and enabling technologies from Pfizer. Effective upon the closing of the transaction on September 20, 2023, Alexion acquired all of Pfizer' s rights under the Pfizer Agreement and became the successor~~ -- **success** ~~-~~ in ~~- interest~~ **performing the functions assigned** to ~~Pfizer thereunder. We refer to the~~ **them in** ~~Pfizer Agreement following the~~ **these arrangements** ~~acquisition, as the Alexion Agreement. The acquisition does not impact the material terms of the option and license agreement. In March 2022, we entered into an option and license agreement with Novartis, or the 2022 Novartis Option and License Agreement, pursuant to which we granted Novartis options to receive an exclusive license to TRACER Capsids to develop and commercialize certain AAV gene therapy candidates comprised of a TRACER Capsid and specified genetic payloads for specific genetic targets. Under the terms of the 2022 Novartis Option and License Agreement, we received an upfront payment of $ 54. 0 million. Effective as of March 1, 2023, Novartis exercised its options to license TRACER Capsids for use in gene therapy programs against two undisclosed neurologic disease targets. With Novartis' option exercise on two targets, we received a $ 25. 0 million option exercise payment in April of 2023, and we are eligible to receive associated potential development, regulatory, and commercial milestone payments, as well as mid- to high- single- digit tiered royalties based on net sales of Novartis products incorporating the licensed capsids. In addition, during the research term, Novartis retains the right to expand the agreement to include options to license capsids for up to two additional rare CNS targets, subject to their availability, for a fee of $ 18. 0 million per target. Under such an expansion, we would be eligible to receive a $ 12. 5 million license option exercise fee for each target exercised, as well as future potential milestone payments per target and mid- to high- single- digit tiered royalties on products incorporating the licensed capsids. Novartis elected not to license a capsid for one CNS target under the 2022 Novartis Option and License Agreement prior to the expiration of the applicable option period. As a result we are no longer eligible to receive development, regulatory, and commercial milestone payments or royalties in connection with this target, and all capsid rights with respect to that target have returned to us~~ . Our current collaborators or any future collaborator might not be successful in obtaining approvals for the product candidates arising from our collaboration or commercializing or manufacturing the resulting products. Further, such collaborator' s objectives in connection with the collaboration may not be consistent with our best interests. With respect to the rights granted to a collaborator by us, the collaborator could take actions that may be adverse to us, or it could halt, slow, or deprioritize its development and commercialization efforts under the collaboration. In any such instances, our business, financial condition, results of operations and prospects could be materially harmed. ~~72We~~ **We** may seek to enter into collaborations ~~,~~ and out- licensing transactions in the future with other third parties. If we are unable to enter into such collaborations or out- licensing transactions, or if these collaborations or out- licensing transactions are not successful, our business could be adversely affected. We may seek to enter into additional collaborations in the future, including sales, marketing, distribution, development, option, licensing, and / or broader collaboration agreements. For example, on January 8, 2023, we entered into a second collaboration agreement, or the 2023 Neurocrine Collaboration Agreement, with Neurocrine for the research, development, manufacture and commercialization of gene therapy products directed to the gene that encodes GBA1, for the treatment of Parkinson' s disease and other diseases associated with ~~GBA1, or~~ the GBA1 Program ~~,~~ and three new programs focused on the research, development, manufacture and commercialization of gene therapies designed to address central nervous system diseases or conditions associated with rare genetic targets, or the 2023 Discovery Programs, and, collectively with the GBA1 Program, the 2023 Neurocrine Programs. On December 28, 2023, we entered into the 2023 Novartis Collaboration Agreement to (a) provide rights to Novartis with respect to certain of our TRACER Capsids for use in the research, development, and commercialization by Novartis of AAV gene therapy products and product candidates, comprising such TRACER Capsids and payloads intended for the treatment of spinal muscular atrophy, or the Novartis SMA Program, and (b) collaborate to develop AAV gene therapy products and product candidates intended for the treatment of Huntington' s disease under the Novartis HD Program, in each case, leveraging our TRACER Capsids and other intellectual property controlled by us. Our likely collaborators, optionees, and licensees include large and mid- size pharmaceutical companies, regional and national pharmaceutical companies, biotechnology companies, and medical device manufacturers. However, we may not be able to enter into additional collaborations or option and license transactions on favorable terms or at all. Our ability to generate revenues from our collaborations and option and license transactions will depend on our and our collaborators', optionees', and licensees' abilities to successfully perform the functions assigned to each of us in these arrangements. In addition, our collaborators, optionees, and licensees might have the ability to abandon research or development projects and terminate applicable agreements. Moreover, an unsuccessful outcome in any clinical trial for which our collaborator, optionee, or licensee is responsible could be harmful to the public perception and prospects of our proprietary antibody program and gene therapy and vectorized antibody platforms. ~~Our~~ **76Our** relationship with any current or future collaborators, optionees, or licensees may pose several risks, including the following: ● collaborators, optionees, and licensees have significant discretion in determining the amount and timing of the efforts and resources that they will apply to these collaborations and option and license transactions; ● collaborators, optionees, or licensees may not perform their obligations as expected or desired; ● the preclinical studies and clinical trials conducted as part of these collaborations or by our licensees may not be successful; ● collaborators, optionees, or licensees may not pursue development and commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs based on preclinical study or clinical trial results, changes in the collaborators', optionees', or licensees' strategic focus or available funding or external factors, such as an acquisition, which divert resources or create competing priorities; ● collaborators, optionees, or licensees may delay preclinical studies and clinical trials, provide insufficient funding for preclinical studies and clinical trials, stop a preclinical study or clinical trial or abandon a product candidate, repeat or conduct new preclinical studies or clinical trials or require a new formulation of a product candidate for preclinical studies or clinical trials; ~~73~~ ● we may not have access to, or may be restricted from disclosing, certain information regarding product candidates being developed or commercialized under a

collaboration or by a licensee and, consequently, may have limited ability to inform our stockholders about the status of such product candidates; ● collaborators, optionees, or licensees could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates if the collaborators, optionees, or licensees believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours; ● product candidates developed in collaboration with us or by a licensee may be viewed by our collaborators or licensees as competitive with their own product candidates or products, which may cause collaborators or licensees to cease to devote resources to the commercialization of our product candidates; ● a collaborator or licensee with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of any such product candidate; ● disagreements with collaborators, optionees, or licensees, including disagreements over proprietary rights, contract interpretation or the preferred course of development of any product candidates, may cause delays or termination of the research, development or commercialization of such product candidates, may lead to additional responsibilities or expenses for us with respect to such product candidates (in the case of collaborations) or may result in litigation or arbitration, any of which would be time- consuming and expensive; ● in collaboration, licensing, and option arrangements where we have licensed intellectual property rights to collaborators, licensees, and optionees who have the right to control prosecution of the licensed intellectual property rights, disputes may arise with respect to the prosecution strategy for the relevant intellectual property rights, which may impair our ability to pursue our preferred prosecution strategy or achieve the desired protection from any relevant patents; **77** ● collaborators, optionees, or licensees may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation; ● disputes may arise with respect to the ownership or inventorship of intellectual property developed pursuant to our collaborations or option and license transactions; ● collaborators, optionees, or licensees may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; ● the terms of our collaboration or license agreement may restrict us from entering into certain relationships with other third parties, thereby limiting our options; and ● collaborations may be terminated for the convenience of the collaborator and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates. Collaboration and license agreements may not lead to the development or commercialization of product candidates in the most efficient manner, or at all. If our collaborations or option and license transactions do not result in the successful development and commercialization of products, or if one of our collaborators, optionees, or licensees terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under ~~74the~~ -- **the** collaboration or option and license transactions. If we do not receive the funding we expect under these agreements, our development of our product candidates could be delayed, and we may need additional resources to develop our product candidates. In the event we are unable to achieve milestones necessary to demonstrate progress on our programs relevant to our ongoing collaborations with Neurocrine or Novartis, Neurocrine or Novartis may be unwilling to fund these programs at the desired levels or at all, which could require us to fund these programs to a greater extent than we have expected, to decline to pursue certain program objectives or to discontinue one or more of the programs. Additionally, subject to its contractual obligations to us, if a collaborator, optionee, or licensee of ours were to be involved in a business combination, it might deemphasize or terminate the development or commercialization of any product candidate optioned or licensed to it by us. If one of our collaborators, optionees, or licensees terminates its agreement with us, we may find it more difficult to attract new collaborators, optionees, or licensees, and 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 periodic report also apply to the activities of our collaborators, optionees, and licensees. We will face significant competition in seeking appropriate collaborators, optionees, and licensees, and the negotiation process is time- consuming and complex. Our ability to reach a definitive collaboration or license agreement with any future collaborators, optionees, and licensees will depend, among other things, upon our assessment of the collaborator' s, optionee' s, or licensee' s resources and expertise, the terms and conditions of the proposed collaboration or option and license transactions and the proposed collaborator' s, optionee' s, or licensee' s evaluation of several factors. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product 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, optionee, or licensee may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration or option and license transaction could be more attractive than the one with us for our product candidate. We may also be restricted under future license agreements from entering into agreements on certain terms with potential collaborators, optionees, or licensees. 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, optionees, and licensees. ~~If~~ **78If** we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms, or at all, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations or option and license transactions and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market or continue

to develop our proprietary antibody program or gene therapy and vectorized antibody platforms and programs. If we license rights to product candidates, 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. We and our collaborators have relied, and we and our collaborators expect to continue to rely, on third parties to conduct, supervise and monitor our preclinical studies and clinical trials, and if these third parties perform in an unsatisfactory manner, our business could be harmed. We and our collaborators expect to rely on CROs, clinical trial sites, and other vendors to ensure our preclinical studies and clinical trials are conducted properly and on time. We and our collaborators may also engage third parties such as clinical data management organizations, medical institutions and clinical investigators to conduct or assist in our clinical trials or other preclinical and clinical research and development work. While we and our collaborators will have agreements governing their activities, we and our collaborators will have limited influence over their actual performance. We and our collaborators will control only certain aspects of our third- party service providers' activities. Nevertheless, we and our collaborators will be responsible for ensuring that each of our preclinical studies and clinical trials is ~~75conducted~~ -- **conducted** in accordance with the applicable protocol, legal, quality, regulatory and scientific standards. Our reliance on these third parties does not relieve us of our regulatory responsibilities. For example, the PD- 1101 Phase 1b clinical trial of VY- AADC (NBIb- 1817) and the separate PD- 1102 Phase 1 clinical trial exploring the delivery of VY- AADC (NBIb- 1817) using a posterior trajectory were conducted at several locations. Additionally, we had expected to initiate the planned VYTAL Phase 1 and 2 clinical trial for VY- HTT01 at multiple sites in the United States before our decision to refocus the Huntington' s disease program. If any locations terminate a particular clinical trial, we or our collaborators would be required to find other parties or locations to conduct such clinical trial. We and our collaborators may be unable to find a new party to conduct new trials of our product candidates or obtain clinical supply of our product candidates or AAV vectors for such trials. If we or our collaborators elect to internalize some or all activities related to the conduct of our preclinical studies or clinical trials that are currently performed by our third- party service providers, or if we or our collaborators are required to do so due to a service provider' s termination of our relationship, then we or our collaborators may be required to source additional technology and personnel in order to perform the relevant activities. We and our collaborators may be unsuccessful in our efforts to internalize some or all relevant activities, either on the desired timeline or at all. We, our collaborators, and our third- party service providers are required to comply with the FDA' s ~~good laboratory practices, or~~ GLPs, and GCPs for conducting, recording and reporting the results of IND- enabling preclinical studies and clinical studies to assure that the data and reported results are credible and accurate and that the rights, integrity and confidentiality of clinical trial participants are protected. We and our collaborators are also required to register ongoing clinical trials and post the results of completed clinical trials on a government- sponsored database, ClinicalTrials. gov, within specified timeframes. The FDA enforces these GLPs and GCPs through periodic inspections of trial sponsors, principal investigators, clinical trial sites, and laboratories at which the FDA may determine that our preclinical studies and clinical trials did not comply with GLPs or GCPs. If we, our collaborators, or our third- party service providers fail to comply with applicable GLPs or GCPs, the preclinical or clinical data generated in our future preclinical studies or clinical trials may be deemed unreliable and the FDA may require us to perform additional preclinical studies or clinical trials before approving the relevant INDs or marketing applications. In addition, our future clinical trials will require a sufficient number of patients to evaluate the safety and effectiveness of our product candidates. Accordingly, if we, our collaborators, or our third- party service providers fail to comply with these regulations or fail to recruit a sufficient number of patients, we may be required to repeat such preclinical studies or clinical trials, which would delay the regulatory approval process. Failure to comply can also result in fines, adverse publicity, and civil and criminal sanctions. ~~Our~~ **79Our** third- party service providers are not our employees, and we and our collaborators are therefore unable to directly monitor whether or not they devote sufficient time, attention, expertise and resources to our clinical and nonclinical programs. These third- party service providers may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other drug development activities that could harm our competitive position. If our third- party service providers do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, or if the quality or accuracy of the preclinical or clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements, or for any other reasons, our preclinical studies or clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize our product candidates. As a result, our financial results and the commercial prospects for our product candidates could be harmed, our costs could increase, and our ability to generate revenues could be delayed. Risks Related to ManufacturingOur gene therapies **, non- viral therapeutics, and other biological products** are novel, complex and difficult to manufacture. We could experience manufacturing problems that result in delays in the development or commercialization of our product candidates or otherwise harm our business. The manufacture of gene therapy **, non- viral therapeutic, and other biological** products is technically complex and necessitates substantial expertise and capital investment. Production difficulties caused by unforeseen events may delay the availability of material for our clinical studies. To meet the requirements of our current and planned future trials we have developed a flexible **AAV gene therapy** manufacturing platform that is based on proprietary technology and provides a scalable process for preclinical and ~~76clinical~~ -- **clinical** AAV production. We are using a HEK 293 based transient transfection manufacturing process to support our preclinical research ~~activities. We also have expertise with the baculovirus / Sf9 AAV production system, a technology for producing AAV gene therapy vectors at scale in insect- derived cells, which we have used for our clinical development activities in the past and may use in the future for clinical development~~ activities. As the field advances, we will continue to evaluate additional novel manufacturing technologies that may be suitable for future clinical and commercial manufacturing. We presently contract with third parties for the manufacturing of our program materials for our proprietary antibody and gene therapy product candidates. We have also built an onsite, state- of- the- art process research and development facility to enable the manufacturing of preclinical AAV gene therapy vectors for large animal studies including IND enabling GLP toxicology materials. We ~~are~~

~~currently assessing our manufacturing capabilities, and we~~ do not currently have our own clinical or commercial scale manufacturing. The use of contract manufacturing and reliance on collaboration partners is relatively cost- efficient and eliminates the need for our direct investment in manufacturing facilities and additional staff early in development. Although we rely on contract manufacturers, we have personnel with manufacturing and quality experience to oversee our contract manufacturers. To date, our third- party manufacturers have met our manufacturing requirements for our program materials. We expect third- party manufacturers to be capable of providing sufficient quantities of our program materials to meet anticipated clinical trial scale demands. To meet our projected needs for clinical and commercial manufacturing, third parties with whom we currently work might need to increase their scale of production **,** or we may need to secure additional suppliers as part of our external manufacturing network. We believe that there are alternate sources of supply for our program materials that can satisfy our clinical and commercial requirements, although we cannot be certain that identifying and establishing relationships and technology transfers with such sources, if necessary, would not result in significant delay or material additional costs. However, if a third- party manufacturer decided to not enter into a new contract with us for program materials or if they did not have the capacity to meet our needs for program materials, we may be required to contract with additional suppliers on terms which may be less favorable to us or would result in additional material costs. To date, our third- party manufacturers have met our quality standards for our program materials. The manufacturers of pharmaceutical products must comply with strictly enforced cGMP requirements, state and federal regulations, as well as foreign requirements when applicable. Any failure by us or our contract manufacturing organizations to adhere to or document compliance to such regulatory requirements could lead to a delay or interruption in the availability of our program materials for clinical study. If we or our manufacturers were to fail to comply with the FDA, EMA, or other regulatory authority, it could result in sanctions being imposed on us, including clinical holds, ~~fines~~ **80fines** , injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates. Our potential future dependence upon others for the manufacture of our product candidates may also adversely affect our future profit margins and our ability to commercialize any product candidates that receive regulatory approval on a timely and competitive basis. Biological products are inherently difficult to manufacture. Our program materials are manufactured using technically complex processes requiring specialized equipment and facilities, highly specific raw materials, cells, and reagents, and other production constraints. Several of these raw materials, cells, and reagents are provided by a limited number of suppliers. Even though we aim to have backup supplies and suppliers of raw materials, cells, and reagents whenever possible, we cannot be certain they will be sufficient if our primary sources are unavailable. A shortage of a critical raw material, cell line, or reagent, or a technical issue during manufacturing may lead to delays in clinical development or commercialization plans. Any changes in the manufacturing of components of the raw materials we use could result in unanticipated or unfavorable effects on our manufacturing processes, including delays. ~~77Delays~~ -- **Delays** in obtaining regulatory approval of our or our collaborators' manufacturing processes and facilities or disruptions in such manufacturing processes may delay or disrupt our commercialization efforts. Until recently, no cGMP gene therapy manufacturing facility in the United States had received approval from the FDA for the manufacture of an approved gene therapy product. Before we can begin to commercially manufacture a product candidate in our own facility, or the facility of a collaborator, we must obtain regulatory approval from the FDA for our manufacturing process and our collaborator' s facility. A manufacturing authorization must also be obtained from the appropriate European Union regulatory authorities. Until recently, no cGMP gene therapy manufacturing facility in the United States had received approval from the FDA for the manufacture of an approved gene therapy product and, therefore, the timeframe required for us to obtain such approval is uncertain. In addition, we must pass a pre- approval inspection of our or our collaborator' s manufacturing facility by the FDA and other relevant regulatory authorities before any of our product candidates can obtain marketing approval. In order to obtain approval, we will need to ensure that all of our processes, methods and equipment are compliant with cGMP, and perform extensive audits of vendors, contract laboratories and suppliers. If any of our vendors, contract laboratories or suppliers is found to be out of compliance with cGMP, we may experience delays or disruptions in manufacturing while we work with these third parties to remedy the violation or while we work to identify suitable replacement vendors. The cGMP requirements govern quality control of the manufacturing process and documentation policies and procedures. In complying with cGMP, we will be obligated to expend time, money and effort in production, record keeping and quality control to assure that the product meets applicable specifications and other requirements. If we fail to comply with these requirements, we would be subject to possible regulatory action and may not be permitted to sell any products that we may develop. Failure to comply with ongoing regulatory requirements could cause us to suspend production or put in place costly or time- consuming remedial measures. The regulatory authorities may, at any time, following approval of a product for sale, audit the manufacturing facilities for such product or institute biennial inspections. If any such inspection or audit identifies a failure to comply with applicable regulations, or if a violation of product specifications or applicable regulations occurs independent of such an inspection or audit, the relevant regulatory authority may require remedial measures that may be costly or time- consuming to implement and that may include the temporary or permanent suspension of a clinical trial or commercial sales or the temporary or permanent closure of a manufacturing facility. Any such remedial measures imposed upon our third- party manufacturers, our collaborators, or us could harm our business, financial condition, results of operations and prospects. If our third- party manufacturers, our collaborators, or we fail to comply with applicable cGMP regulations, FDA and foreign regulatory authorities can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new product candidate or suspension or revocation of a pre- existing approval. Such an occurrence may cause our business, financial condition, results of operations and prospects to be harmed. ~~Additionally~~ **81Additionally** , if supply from any third- party manufacturers is delayed or interrupted, there could be a significant disruption in the supply of our clinical or commercial material. We have agreements in place with our contract manufacturers pursuant to which we are collaborating on cGMP manufacturing processes and analytical methods for the

manufacture of our proprietary antibody and AAV product candidates. **However, we are dependent on one third- party manufacturer to produce our AAV and one for the tau antibody clinical product candidates.** Therefore, if we are unable to enter into an agreement with our contract manufacturers to manufacture clinical or commercial material for our product programs, or if our agreement with our contract manufacturers were terminated, we would have to find suitable alternative manufacturers. This could delay our or our collaborators' ability to conduct clinical trials or commercialize our current and future product candidates. The regulatory authorities also may require additional trials if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and could result in a delay in our desired clinical and commercial timelines. ~~78Any~~ -- **Any** contamination in the manufacturing process for our products or product candidates, shortages of raw materials, cells or reagents, or failure of any of our key suppliers to deliver necessary components could result in delays in our clinical development or marketing schedules. Given the nature of biologics manufacturing, there is a risk of contamination. Any contamination could adversely affect our ability to produce product candidates on schedule and could, therefore, harm our results of operations and cause reputational damage. Some of the raw materials required in our manufacturing process are derived from biologic sources. Such raw materials are difficult to procure and may be subject to contamination or recall. A material shortage, contamination, recall or restriction on the use of biologically derived substances in the manufacture of our product candidates could adversely impact or disrupt the commercial manufacturing or the production of clinical material, which could adversely affect our development timelines and our business, financial condition, results of operations and prospects. Failure to obtain access to or to protect intellectual property related to the manufacturing of our products or product candidates may result in changes, delays and / or inability to manufacture such products or product candidates. The intellectual property related to the manufacture of biological products is complex. If we are unable to maintain control of manufacturing technology such as our trade secrets, or we are unable to protect ongoing improvements comprehensively and in a sufficient number of jurisdictions, it would impact our ability to produce products for commercial sale or product candidates for preclinical testing or clinical trials and our development timelines and operations timelines could be adversely affected. We presently manufacture our AAV product candidates using a mammalian cell system. We are aware of third parties which also use this system in the manufacture of their products and who hold intellectual property on their AAV manufacturing systems. If we determine that access to certain third- party intellectual property is necessary for the manufacturing of our products and product candidates and are unable to license or otherwise access this intellectual property, it would impact our ability to produce products for commercial sale or product candidates for preclinical testing or clinical trials and our development timelines and operations timelines could be adversely affected. Risks Related to Our Business OperationsWe may not be successful in our efforts to identify or discover additional product candidates and may fail to capitalize on programs or product candidates that may be a greater commercial opportunity, or for which there is a greater likelihood of success. The success of our business depends upon our ability to identify, develop and commercialize product candidates generated through our proprietary antibody program and our gene therapy ~~and~~ **,** vectorized antibody **, and non- viral therapeutics** platforms and programs. Research programs to identify new product candidates require substantial technical, financial and human resources. ~~Our~~ **Most of our** product candidates are in preclinical development **, and one is in early- stage clinical trials** . Our current portfolio of product candidates is subject to change as we continue to conduct preclinical **and clinical** testing and to develop product candidates and prioritize or abandon product candidates based on ~~such~~ **82such** results and other factors. For example, ~~in August 2022,~~ we ~~announced a re~~ **are** ~~- prioritization of~~ **no longer advancing VY9323, formerly the lead development candidate for** our ~~portfolio~~ **SOD1 silencing program for ALS, as a development candidate and are assessing alternate payloads for the program** based on **three- month data from** a ~~review evaluating our programs based on non -~~ ~~, among other things, our assessment of their potential for competitive differentiation, the efficiency of such product candidate' s path to~~ human ~~proof of biology~~ **primate GLP toxicology study suggesting that a different payload would be necessary to achieve the desired product profile** ~~or~~ **for** ~~proof of mechanism (reflecting~~ the **program** ~~availability of validated biomarkers), unmet medical need, commercial opportunity, and alignment with our overall strategy, as well as supportive preclinical data~~ . We may also fail to identify other product candidates for clinical development for several reasons. For example, our research may be unsuccessful in identifying potential product candidates or our potential product candidates may be shown to have harmful side effects, may be commercially impracticable to manufacture or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval. Additionally, because we have limited resources, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential. Similar to our prior investments with regard to our VY- AADC (NBIb- 1817) and VY- HTT01 programs, our spending on current and ~~79future~~ -- **future** research and development programs may not yield any commercially viable products. If we do not accurately evaluate the commercial potential for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaboration, option and license, or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. Alternatively, we may allocate internal resources to a product candidate in a therapeutic area in which it would have been more advantageous to enter into a ~~partnering~~ **licensing or collaboration** arrangement. Several of our current preclinical programs have previously been part of collaborations with third parties. While we have invested significant resources in these programs, we may decide in the future to cease development activities on one or more of them. If any of these events occur, we may be forced to abandon our development efforts with respect to a particular product candidate or fail to develop a potentially successful product candidate, which could harm our business, financial condition, results of operations and prospects. Our future success depends on our ability to retain key members of our management and research and development teams, and to attract, retain and motivate qualified personnel. We are highly dependent on the management, technical, and scientific expertise of principal members of our management, scientific, and clinical teams. While we have entered into employment agreements or offer letters with each of our executive officers, any of them could leave our employment at any

time, as all of our employees are " at will " employees. We currently do not have " key person " insurance on any of our employees. The loss of the services of one or more of our current employees might impede the achievement of our research, development and commercialization objectives. Recruiting and retaining qualified employees, consultants and advisors for our business, including scientific and technical personnel, is critical to our success. There currently is a shortage of skilled individuals with substantial gene therapy experience, which is likely to continue. As a result, competition for skilled personnel, including in gene therapy research and vector manufacturing, is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms, if at all, given the competition among numerous pharmaceutical and biotechnology companies and academic institutions for individuals with similar skill sets. 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. In addition, failure to succeed in preclinical or clinical trials or applications for marketing approval, the termination of relationships with collaborators, and the reduction of our workforce in connection with the development of a new portfolio and platform strategy may make it more challenging to recruit and retain qualified personnel. The inability to recruit, or loss of services of, certain executives, key employees, consultants or advisors, may impede the progress of our research, development and commercialization objectives and could harm our business, financial condition, results of operations and prospects. ~~If~~ **83If** we are unable to manage expected growth in the scale and complexity of our operations, our performance may suffer. If we are successful in executing our business strategy, we will need to expand our managerial, operational, financial and other systems and resources to manage our operations, continue our research and development activities and, in the longer term, build a commercial infrastructure to support commercialization of any of our product candidates that are approved for sale. We can provide no assurances that we will have sufficient resources in the future to manage all of our planned programs. Future growth would impose significant added responsibilities on members of management, may lead to significant added costs, and may divert our management and business development resources. It is likely that our management, finance, development personnel, systems and facilities currently in place may not be adequate to support this future growth. Our need to effectively manage our operations, growth and product candidates requires that we continue to develop more robust business processes and improve our systems and procedures in each of these areas and to attract and retain sufficient numbers of talented employees. We may be unable to successfully implement these tasks on a larger scale and, accordingly, may not achieve our research, development and growth goals. ~~80Our~~ -- **Our** employees, principal investigators, consultants and commercial partners may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading. We are exposed to the risk of fraud or other misconduct by our employees, principal investigators, consultants, collaborators, and commercial partners. Misconduct by these parties could include intentional failures to comply with FDA regulations or the regulations applicable in the European Union and other jurisdictions, provide accurate information to the FDA, the European Commission and other regulatory authorities, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self- dealing and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct also could involve the improper use of information obtained in the course of clinical trials or interactions with the FDA or other regulatory authorities, which could result in regulatory sanctions and cause serious harm to our reputation. We have adopted a code of conduct applicable to all of our employees, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from government investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, financial condition, results of operations and prospects, including the imposition of significant fines or other sanctions. Current and future legislation may increase the difficulty and cost for us and any collaborators to obtain marketing approval of and commercialize our product candidates and affect the prices we, or they, may obtain. In the United States and 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 product candidates, restrict or regulate post- approval activities and affect our ability, or the ability of any collaborators, to profitably sell any products for which we obtain marketing approval. We expect that current laws, 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, or any collaborators, may receive for any approved products. If reimbursement of our products is unavailable or limited in scope, our business could be materially harmed. In March 2010, President Obama signed the ACA into law. In addition, other legislative changes have been proposed and adopted since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $ 1. 2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation' s automatic reduction to several government programs. These changes included aggregate reductions to Medicare payments to providers of up to 2 % per fiscal year, which went into effect in ~~April~~ **84April** 2013 and will remain in effect through ~~2030~~ **2032** under the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act. The American Taxpayer Relief Act of 2012, 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. These laws may result in additional reductions in Medicare and other healthcare funding and otherwise affect the prices we may obtain for any of our product candidates for which we may obtain regulatory approval or the frequency with which any such product candidate is prescribed or used. Since enactment of the ACA, there have been, and

continue to be, numerous legal challenges and Congressional actions to repeal and replace provisions of the law. For example, with enactment of the Tax Cuts and Jobs Act of 2017, or the TCJA, which was signed by President Trump on December 22, 2017, Congress repealed the " individual mandate. " The repeal of this provision, which requires most Americans to carry a minimal level of health insurance, became effective in 2019. Further, ~~on December 14, 2018, a U. S. District Court judge~~ in ~~the Northern District of Texas ruled that the individual mandate portion of the ACA is an essential and inseverable feature of the ACA, and therefore because the mandate was repealed as part of the TCJA, the remaining provisions of the ACA are invalid as well. On December 18, 2019, the Court of Appeals for the Fifth Circuit affirmed the lower court' s ruling that the individual mandate portion of 81the ACA is unconstitutional and it remanded the case to the district court for reconsideration of the severability question and additional analysis of the provisions of the ACA. Thereafter, the U. S. Supreme Court agreed to hear this case. Oral argument in the case took place on November 10, 2020. On~~ June ~~17,~~ 2021, the **United States** ~~U. S.~~ Supreme Court dismissed **the most recent judicial** ~~this case after finding that plaintiffs do not have standing to~~ challenge **to the ACA brought by several states without specifically ruling on** the constitutionality of the ~~ACA~~ **statute**. Litigation and legislation over the ACA are likely to continue, with unpredictable and uncertain results. ~~The~~ **During the first** Trump Administration ~~also took~~ **, the Congress and administration sought to overturn the ACA and related measures. Shortly after taking office in January 2025, President Trump revoked numerous** executive **orders issued by** ~~actions to undermine or delay implementation of the ACA, including directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On January 28, 2021, however,~~ President Biden ~~issued a new~~ **, including at least two** ~~Executive~~ **executive** ~~Order which directs federal agencies to reconsider rules~~ **orders (e. g., EO 14009, Strengthening Medicaid** and ~~other~~ ~~--~~ **the** ~~policies that limit~~ **Affordable Care Act, and EO 14070, Continuing to Strengthen** Americans' ~~access~~ **Access** to **Affordable, Quality** ~~health~~ **Health** ~~care~~ **Coverage) where were designed to further implement the ACA. We anticipate similar efforts to undermine the ACA**, and ~~consider actions~~ **the accompanying uncertainty, for the foreseeable future. We expect** that **these healthcare reforms, as** ~~will~~ **well** ~~protect and strengthen~~ **as other healthcare reform measures** that ~~access. Under this Executive Order~~ **may be adopted in the future**, ~~federal agencies~~ **may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and additional downward pressure on the price that we receive for any approved product and / or the level of reimbursement physicians receive for administering any approved product we might bring to market. Reductions in reimbursement levels may negatively impact the prices we receive or the frequency with which our products** are ~~directed to re- examine: policies~~ **prescribed or administered. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. Accordingly, such reforms, if enacted, could have an adverse effect on anticipated revenue from product candidates** that **we** ~~undermine protections for people with pre- existing conditions, including complications related to COVID- 19; demonstrations and waivers under Medicaid and the ACA that~~ may ~~reduce coverage~~ **successfully develop and** ~~or~~ **for which we may obtain marketing approval and may affect** ~~undermine the programs, including work requirements; policies that undermine the Health Insurance Marketplace or~~ **our overall** ~~other markets for health insurance; policies that make it more difficult to enroll in Medicaid and the ACA; and policies that reduce affordability of coverage or~~ financial ~~assistance, including~~ **condition and ability to develop** ~~for~~ ~~-~~ **or** ~~dependents~~ **commercialize product candidates**. The prices of prescription pharmaceuticals in the United States and foreign jurisdictions are subject to considerable legislative and executive actions and could impact the prices we obtain for our drug products, if and when approved. The prices of prescription pharmaceuticals have also been the subject of considerable discussion in the United States and other jurisdictions. To date, there have been several ~~recent~~ U. S. congressional inquiries, as well as proposed and enacted state and federal legislation designed to, among other things, bring more transparency to pharmaceutical pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of pharmaceuticals under Medicare and Medicaid, and reform government program reimbursement methodologies for products ~~. In 2020, former President Trump issued several executive orders intended to lower the costs of prescription products and certain provisions in these orders have been incorporated into regulations. These regulations include an interim final rule implementing a most favored nation model for prices that would tie Medicare Part B payments for certain physician- administered pharmaceuticals to the lowest price paid in other economically advanced countries, effective January 1, 2021. That rule, however, has been subject to a nationwide preliminary injunction and, on December 29, 2021, the Centers for Medicare & Medicaid Services, or CMS, issued a final rule to rescind it. With issuance of this rule, CMS stated that it will explore all options to incorporate value into payments for Medicare Part B pharmaceuticals and improve beneficiaries' access to evidence- based care~~. In addition, in October 2020, the Department of Health and Human Services, or the HHS and the FDA published a final rule allowing states and other entities to develop a Section 804 Importation Program, or SIP, to import certain prescription drugs from Canada into the United States. That regulation was challenged in a lawsuit by the Pharmaceutical Research and Manufacturers of America, or PhRMA, but the case was dismissed by a federal district court in February 2023 after the court found that PhRMA did not have standing to sue HHS. ~~Nine~~ **Five** states ( ~~Vermont,~~ Colorado, Florida, Maine, **New Hampshire and** New Mexico ~~, New Hampshire, North Dakota, Texas, and Wisconsin~~ ) ~~have passed laws allowing for the importation of drugs from Canada. Certain of these states~~ have submitted Section 804 Importation Program proposals **to the** ~~and are awaiting~~ FDA ~~approval. On~~ **, and, on** January 5, ~~2023~~ **2024**, the FDA approved Florida' s plan for Canadian drug importation. **That state now has authority to import certain drugs from Canada for a period of two years once certain conditions are met. Florida will first need to submit a pre-import request for each drug selected for importation, which must be approved by the FDA. The state will also need to relabel the drugs and perform quality testing of the products to meet FDA standards.** ~~Further~~ **85Further**, in November 2020, the HHS finalized 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. The Inflation Reduction Act of 2022, or IRA, further delayed implementation of this rule to January 1, 2032 ~~. 82In July 2021, President Biden signed Executive Order 14063, which focuses on, among other things, the price of pharmaceuticals. The order directed the HHS to create a plan within 45 days to combat " excessive pricing of prescription pharmaceuticals and enhance domestic pharmaceutical supply chains, to reduce the prices paid by the federal government for such pharmaceuticals, and to address the recurrent problem of price gouging. " In September 2021, the HHS released its plan to reduce pharmaceutical prices. The key features of that plan are to: (a) make pharmaceutical prices more affordable and equitable for all consumers and throughout the health care system by supporting pharmaceutical price negotiations with manufacturers; (b) improve and promote competition throughout the prescription pharmaceutical industry by supporting market changes that strengthen supply chains, promote biosimilars and generic drugs, and increase transparency; and (c) foster scientific innovation to promote better healthcare and improve health by supporting public and private research and making sure that market incentives promote discovery of valuable and accessible new treatments~~ . More recently, on August 16, 2022, the IRA was signed into law by President Biden. The new legislation has implications for Medicare Part D, which is a program available to individuals who are entitled to Medicare Part A or enrolled in Medicare Part B to give them the option of paying a monthly premium for outpatient prescription drug coverage. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023); and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. Specifically, with respect to price negotiations, Congress authorized Medicare to negotiate lower prices for certain costly single- source drug and biologic products that do not have competing generics or biosimilars and are reimbursed under Medicare Part B and Part D. CMS may negotiate prices for ten high- cost drugs paid for by Medicare Part D starting in 2026, followed by 15 Part D drugs in 2027, 15 Part B or Part D drugs in 2028, and 20 Part B or Part D drugs in 2029 and beyond. This provision applies to drug products that have been approved for at least 9 years and biologics that have been licensed for 13 years, but it does not apply to drugs and biologics that have been approved for a single rare disease or condition. Nonetheless, since CMS may establish a maximum price for these products in price negotiations, we would be fully at risk of government action if our products became the subject of Medicare price negotiations. Moreover, given the risk that could be the case, these provisions of the IRA may also further heighten the risk that we would not be able to achieve the expected return on any drug products or full value of our patents protecting our products if prices are set after such products have been on the market for nine years. Further, the legislation subjects drug manufacturers to civil monetary penalties and a potential excise tax for failing to comply with the legislation by offering a price that is not equal to or less than the negotiated " maximum fair price " under the law or for taking price increases that exceed inflation. The ~~legislation~~ **IRA** also **established inflation rebate programs under Medicare Part B and Part D. These programs** ~~requires~~ **require** manufacturers to pay rebates **to** ~~for drugs in~~ Medicare **if they raise their prices for certain Part B and** Part D ~~whose price increases exceed~~ **drugs faster than the rate of** inflation **. On December 9, 2024, with issuance of its 2025 Physician Fee Schedule final regulation, CMS finalized its rules governing the IRA inflation rebate programs** . The new law also caps Medicare out- of- pocket drug costs at an estimated $ 4, 000 a year in 2024 and, thereafter beginning in 2025, at $ 2, 000 a year. In addition, the IRA potentially raises legal risks with respect to individuals participating in a Medicare Part D prescription drug plan who may experience a gap in coverage if they required coverage above their initial annual coverage limit before they reached the higher threshold, or " catastrophic period " of the plan. Individuals requiring services exceeding the initial annual coverage limit and below the catastrophic period must pay 100 % of the cost of their prescriptions until they reach the catastrophic period. Among other things, the IRA contains many provisions aimed at reducing this financial burden on individuals by reducing the co- insurance and co- payment costs, expanding eligibility for lower income subsidy plans, and price caps on annual out- of- pocket expenses, each of which could have potential pricing and reporting implications. **The first cycle of negotiations for the Medicare Drug Price Negotiation Program commenced in the summer of 2023. On August 15, 2024, the HHS published the results of the first Medicare drug price negotiations for ten selected drugs that treat a range of conditions, including diabetes, chronic kidney disease, and rheumatoid arthritis. The prices of these ten drugs will become effective January 1, 2026. On January 17, 2025, CMS announced its selection of 15 additional drugs covered by Part D for the second cycle of negotiations. Thereafter, following the change in administrations, CMS issued a public statement on January 29, 2025, declaring that lowering the cost of prescription drugs is a top priority of the new administration and CMS is committed to considering opportunities to bring greater 86transparency in the negotiation program. The second cycle of negotiations with participating drug companies is expected to occur during 2025, and any negotiated prices for this second set of drugs will be effective starting January 1, 2027.** On June 6, 2023, Merck & Co. filed a lawsuit against the HHS and CMS asserting that, among other things, the IRA' s Drug Price Negotiation Program for Medicare constitutes an uncompensated taking in violation of the Fifth Amendment of the Constitution. Subsequently, a number of other parties, including the U. S. Chamber of Commerce, Bristol Myers Squibb Company, the PhRMA, Astellas, Novo Nordisk, Janssen Pharmaceuticals, Novartis, AstraZeneca and Boehringer Ingelheim, also filed lawsuits in various courts with similar constitutional claims against the HHS and CMS. **HHS has generally won the substantive disputes in these cases, and various federal district court judges have expressed skepticism regarding the merits of the legal arguments being pursued by the pharmaceutical industry. Certain of these cases are now on appeal and, on October 30, 2024, the Court of Appeals for the Third Circuit heard oral argument in three of**

**these cases.** We expect that litigation involving these and other provisions of the IRA will continue, with unpredictable and uncertain results. ~~83Accordingly --~~ **Accordingly** , while it is currently unclear how the IRA will be effectuated, we cannot predict with certainty what impact any federal or state health reforms will have on us, but such changes could impose new or more stringent regulatory requirements on our activities or result in reduced reimbursement for our products, any of which could adversely affect our business, results of operations and financial condition. At the state level, individual states are increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, health care organizations 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 health care programs. These measures could reduce the ultimate demand for our products, once approved, or put downward pressure on our product pricing. We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our product candidates or additional pricing pressures **. This may be increasingly true with respect to products approved pursuant to the accelerated approval pathway. State Medicaid programs and other payers are developing strategies and implementing significant coverage barriers, or refusing to cover these products outright, arguing that accelerated approval drugs have insufficient or limited evidence despite meeting the FDA' s standards for accelerated approval** . In other countries, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control and access. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we, or our collaborators, may be required to conduct a clinical trial that compares the cost-effectiveness of our products or product candidates to other available therapies. If reimbursement of our products or product candidates is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be materially harmed. These measures, as well as others adopted in the future, may result in additional downward pressure on the price that we receive for any approved product we or our collaborators might bring to market. Accordingly, such reforms, if enacted, could have an adverse effect on anticipated revenue from that we, or our collaborators, may successfully develop and for which we, or they, may obtain marketing approval and may affect our overall financial condition and ability to develop or commercialize product candidates. ~~Our~~ **87Our** relationships with healthcare providers, physicians and third- party payors will be subject, directly or indirectly, to applicable anti- kickback, fraud and abuse and other healthcare laws and regulations, which, in the event of a violation, could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings. Healthcare providers, physicians and third- party payors will play a primary role in the recommendation and prescription and use of our products and any product candidates for which we obtain marketing approval. Our future arrangements with healthcare providers, physicians and third- party payors 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 market, sell and distribute any products for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations include the following: ● the federal Anti- Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation or arranging of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid; ● the federal False Claims Act imposes criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for, among other things, knowingly presenting, or causing to be presented, false or fraudulent claims for payment by a federal healthcare program or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government, with potential liability including mandatory treble damages and significant per- claim penalties; ~~84~~ ● the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters; ● HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, and its implementing regulations, also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information; ● the federal Physician Payments Sunshine Act requires applicable manufacturers of covered products to report payments and other transfers of value to physicians, other healthcare providers, and teaching hospitals; and ● analogous state and foreign laws and regulations, such as state anti- kickback, false claims, and transparency laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non- governmental third- party payors, including private insurers. Some state laws require pharmaceutical companies to comply with the pharmaceutical industry' s voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and may require product manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures. State and foreign laws also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts. If our operations or the operations of our present and future collaborators are found to be in violation of any of the laws described above or any government regulations that apply to us or them, we or they may be subject to penalties, including civil and criminal penalties, damages, fines, and the curtailment or restructuring of our operations. Any penalties, damages, fines, curtailment or restructuring of our operations could adversely affect our or their financial results. We are developing and implementing a corporate compliance program designed to ensure that we will market and sell any future products that we successfully develop

from our product candidates in compliance with all applicable laws and regulations, but we cannot guarantee that this program will protect us from governmental investigations or ~~other~~ **88other** actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions. Efforts to ensure that our business with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. For example, we are engaged in an ongoing effort to improve our healthcare compliance program and establish a more robust compliance infrastructure. We may fail to establish appropriate compliance measures, and even with a stronger program in place, it is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations 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 these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion of products from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs. 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 other jurisdictions. The provision of benefits or advantages to physicians is governed by anti **-** bribery laws of European Union Member States and the UK Bribery Act 2010. Payments made to physicians in certain European Union Member States must be publicly disclosed and often must be the subject of prior notification and approval by the physician' s employer, his or her competent professional ~~85organization~~ -- **organization** and / or the regulatory authorities of the individual European Union Member States. Failure to comply with these requirements could result in reputational risk, public reprimands, administrative penalties, fines or imprisonment. We are subject to stringent privacy laws, information security laws, regulations, policies and contractual obligations related to data privacy and security and changes in such laws, regulations, policies, and contractual obligations or our failure to comply with such requirements could subject us to significant fines and penalties, which may have a material adverse effect on our business, financial condition or results of operations. We are subject to data privacy and protection laws and regulations that apply to the collection, transmission, storage and use of personally- identifying information, which among other things, impose certain requirements relating to the privacy, security and transmission of personal information, including comprehensive regulatory systems in the United States, European Union, and United Kingdom. The legislative and regulatory landscape for privacy and data protection continues to evolve in jurisdictions worldwide, and there has been an increasing focus on privacy and data protection issues with the potential to affect our business. Failure to comply with any of these laws and regulations could result in enforcement action against us, including fines, imprisonment of company officials and public censure, claims for damages by affected individuals, costly changes to our business practices, damage to our reputation and loss of goodwill, any of which could have a material adverse effect on our business, financial condition, results of operations or prospects. There are numerous U. S. federal and state laws and regulations related to the privacy and security of personal information. In particular, regulations promulgated pursuant to HIPAA establish privacy and security standards that limit the use and disclosure of individually identifiable health information, or protected health information that we may obtain directly or indirectly from health care providers, health plans or other health care industry stakeholders and require the implementation of administrative, physical and technological safeguards to protect the privacy of protected health information and ensure the confidentiality, integrity and availability of electronic protected health information. Determining whether we handle protected health information and whether it has been handled in compliance with applicable privacy standards and our contractual obligations can be complex and may be subject to changing interpretation. These obligations may be applicable to some or all of our business activities now or in the future. ~~In~~ **89In** 2018, California passed into law the California Consumer Privacy Act, or CCPA, which took effect on January 1, 2020 **,** and imposed many requirements on certain businesses that process the personal information of California residents. Many of the CCPA' s requirements are similar to those found in the European Union' s General Data Protection Regulation, or GDPR, including requiring businesses to provide notice to data subjects regarding the information collected about them and how such information is used and shared, and providing data subjects the right to request access to such personal information and, in certain cases, request the erasure of such personal information. The CCPA also affords California residents the right to opt- out of " sales " of their personal information. The CCPA prescribes significant penalties for companies that violate its requirements. On November 3, 2020, California voters passed a ballot initiative for the California Privacy Rights Act, or CPRA, which went into effect on January 1, 2023 and significantly expanded the CCPA to incorporate additional GDPR- like provisions including requiring that the use, retention, and sharing of personal information of California residents be reasonably necessary and proportionate to the purposes of collection or processing, granting additional protections for sensitive personal information, and requiring greater disclosures related to notice to residents regarding retention of information. The CPRA also created a new enforcement agency – the California Privacy Protection Agency – whose sole responsibility is to enforce the CPRA, which will further increase compliance risk. The CPRA may apply to some of our business activities. In addition **to California** , **at least 18** other states ~~, including Connecticut, Colorado, Florida, Indiana, Iowa, Montana, New Jersey, Tennessee, Texas, Utah, and Virginia,~~ have ~~recently~~ passed ~~state~~ **comprehensive** privacy laws ~~;~~ **similar to** the **CCPA and CPRA. These** laws ~~in Connecticut, Colorado, Utah, and Virginia became effective in 2023, the laws in Florida, Montana, and Texas~~ are ~~scheduled to~~ **either in effect or will** go into effect ~~later in~~ **sometime before the end of** ~~2024~~ **2026 . Like the CCPA and CPRA** , ~~the~~ **these** laws ~~in Iowa~~ **create obligations related to the processing of personal information** , ~~New Jersey, and Tennessee~~ **as well as special obligations for the processing of " sensitive " data (which includes health data in some cases). Some of the provisions of these laws may apply to our business activities. There** are ~~scheduled to~~ **also states that are considering or have already passed**

**comprehensive privacy laws that will** go into effect in 2025 ~~,~~ and ~~the~~ **beyond. There are also states that are specifically regulating health information that may affect our business. For example, Washington state recently passed a health privacy** law **that will regulate** ~~in Indiana is scheduled to go into effect in 2026. Congress, at the federal level, and other states are expected to consider similar~~ **collection and sharing of health information, and the** ~~laws~~ **law** ~~in~~ **also has a private right of action, which further increases** the ~~future~~ **relevant compliance risk** . These laws may impact our business activities, including our identification of research subjects, relationships with business partners and ultimately the marketing and distribution of our products **. Plaintiffs' lawyers are also increasingly using privacy- related statutes at both the state and federal level to bring lawsuits against companies for their data- related practices. In particular, there have been a significant number of cases filed against companies for their use of pixels and other web trackers. These cases often allege violations of the California Invasion of Privacy Act and other state laws regulating wiretapping, as well as the federal Video Privacy Protection Act. The rise in these types of lawsuits creates potential risk for our business** . The collection, use, disclosure, transfer, or other processing of personal data regarding individuals in the European Union, including personal health data, is subject to the GDPR, which became effective on May 25, 2018. The ~~86GDPR~~ **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 has been and will continue to require a rigorous and time- intensive process that has increased and will continue to increase our cost of doing business or require us to change our business practices. Despite those efforts, there is a risk that we or our collaborators may be subject to fines and penalties, litigation, and reputational harm in connection with any activities occurring in the European Union, which could adversely affect our business, prospects, financial condition and results of operations. GDPR restrictions on transfers of personal data from the European Union to the United States are unsettled and may impact our business operations. The GDPR generally prohibits transfers of personal data of European Union data subjects outside of the European Union, unless a lawful data transfer solution has been implemented **,** or a specific exception applies. In July 2020, the European Court of Justice invalidated the Privacy Shield program, a voluntary self- ~~certification~~ **90certification** privacy protection mechanism that facilitated transfers of personal data from the European Union to the United States. The court upheld the validity of an alternative contractual mechanism for such data transfers but required companies to take additional steps, such as evaluating supplementary measures that may need to be taken to protect the transferred personal data. In October 2022, President Biden signed an executive order to implement the European Union- U. S. Data Privacy Framework, which would replace the Privacy Shield. In December 2022, the European Commission began the European Union' s process for adopting the European Union- U. S. Data Privacy Framework, but it is unclear if and when the framework will be finalized and whether it will be challenged in court. Continued uncertainty relating to European Union- U. S. data transfers may adversely impact our business operations in the European Union. Beyond GDPR, there are privacy and data security laws in a growing number of countries around the world. Following the exit of the United Kingdom, or UK, from the European Union, the United Kingdom' s Data Protection Act of 2018 applies to the processing of personal data that takes place in the UK and includes parallel obligations to those set forth by GDPR. Privacy and data security laws in several other countries loosely follow GDPR as a model but often contain different or conflicting provisions. These laws will impact our ability to conduct our business activities, including both our clinical trials and any eventual commercialization and distribution of commercial products, through increased compliance costs, costs associated with contracting and potential enforcement actions. Any failure to comply with data protection and privacy laws could result in government- imposed fines or orders requiring that we change our practices, claims for damages or other liabilities, regulatory investigations and enforcement action, litigation and significant costs for remediation, any of which could adversely affect our business. Even if we are not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could harm our business, financial condition, results of operations or prospects. Product liability lawsuits against us could cause us to incur substantial liabilities and could limit commercialization of any product candidates that we may develop. We face an inherent risk of product liability exposure related to the testing of our product candidates in clinical trials and may face an even greater risk if we commercialize any products that we may develop. If we cannot successfully defend ourselves against claims that our product candidates caused injuries, we could incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in: ● decreased demand for any product candidates that we may develop; ● loss of revenue; ~~87~~ ● substantial monetary awards to trial participants or patients; ● significant time and costs to defend the related litigation; ● withdrawal of clinical trial participants; ● the inability to commercialize any product candidates that we may develop; and ● injury to our reputation and significant negative media attention. Although we maintain clinical trial liability insurance in the amount of $ 10. 0 million per occurrence and $ 10. 0 million in the aggregate, this insurance may not be adequate to cover all liabilities that we may incur. We anticipate that we will need to increase our insurance coverage each time we commence a clinical trial. In addition, if we successfully commercialize any product candidate, we will need to obtain product liability insurance. 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~~ **91If** we, our collaborators, or any third- party manufacturers engaged by us or our collaborators fail to comply with environmental, health and safety laws and regulations, we

could become subject to fines or penalties or incur costs that could harm our business. We, our collaborators, and any third-party manufacturers we engage are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the generation, handling, use, storage, treatment, manufacture, transportation and disposal of, and exposure to, hazardous materials and wastes, as well as laws and regulations relating to occupational health and safety. Our operations involve the use of hazardous and flammable materials, including chemicals and biologic and radioactive 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 or from any other work- related injuries, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties. Although we maintain general liability insurance and workers' compensation insurance for certain costs and expenses **,** we may incur due to injuries to our employees resulting from the use of hazardous materials or other work- related injuries, 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 biologic, 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, which have tended to become more stringent over time. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions or liabilities, which could harm our business, financial condition, results of operations and prospects. Further, with respect to the operations of any current or future collaborators or third- party contract manufacturers, it is possible that if they fail to operate in compliance with applicable environmental, health and safety laws and regulations or properly dispose of wastes associated with our products, we could be held liable for any resulting damages, suffer reputational harm or experience a disruption in the manufacture and supply of our product candidates or products. ~~88Risks --~~ **Risks** Related to the Commercialization of Our Product CandidatesThe affected populations for our product candidates may be smaller than we or third parties currently project, which may affect the addressable markets for our product candidates. Our projections of the number of people who have the diseases we are seeking to treat, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are estimates based on our knowledge and understanding of these diseases. The total addressable market opportunity for our product candidates will ultimately depend upon a number of factors including the diagnosis and treatment criteria included in the final label, if approved for sale in specified indications, acceptance by the medical community, patient access and product pricing and reimbursement. Prevalence estimates are frequently based on information and assumptions that are not exact and may not be appropriate, and the methodology is forward- looking and speculative. The process we have used in developing an estimated prevalence range for the indications we are targeting has involved collating limited data from multiple sources. While we believe these sources are reliable, we have not independently verified the data. Accordingly, the prevalence estimates included in our periodic reports and other reports filed with or furnished to the Securities and Exchange Commission, or SEC, should be viewed with caution. Further, the data and statistical information used in such reports, including estimates derived from them, may differ from information and estimates made by our competitors or from current or future studies conducted by independent sources. The use of such data involves risks and uncertainties, and such data is subject to change based on various factors. Our estimates may prove to be incorrect **,** and new studies may change the estimated incidence or prevalence of ~~the~~ **92the** diseases we seek to address. The number of patients with the diseases we are targeting in the United States, the European Union and elsewhere may turn out to be lower than expected or may not be otherwise amenable to treatment with our products, or new patients may become increasingly difficult to identify or access, all of ~~which would harm our results of operations and our business. Additionally, because some patients with the diseases we are targeting in the United States, the European Union, and elsewhere may have increased susceptibility to COVID- 19, the recent COVID- 19 pandemic could limit the number of patients willing to participate in clinical trials related to our products or amenable to treatment with our products,~~ which would harm our results of operations and our business. If we are unable to establish sales, medical affairs and marketing capabilities or enter into agreements with third parties to market and sell our product candidates, we may be unable to generate any product revenue. To successfully commercialize any products that may result from our clinical development programs, we will need to further develop these capabilities, either on our own or with others. The establishment and development of our own commercial team or the establishment of a contract sales force to market any products we may develop will be expensive and time- consuming and could delay any product launch. Moreover, we cannot be certain that we will be able to successfully develop this capability. Under the 2019 Neurocrine Collaboration Agreement, Neurocrine agreed to fund the clinical development through the readout of the RESTORE- 1 Phase 2 clinical trial for VY- AADC (NBIb- 1817). If Neurocrine had not terminated the 2019 Neurocrine Collaboration Agreement with respect to VY- AADC (NBIb- 1817), after the data readout of the RESTORE- 1 Phase 2 clinical trial, we would have had the option to either: (1) co- commercialize VY-AADC (NBIb- 1817) with Neurocrine in the United States under a 50 / 50 cost- and profit- sharing arrangement and receive milestones and royalties based on ex- U. S. sales, or (2) retain the right to receive milestone payments and royalties based on global sales pursuant to the full global commercial rights granted to Neurocrine. Under the terms of the 2019 Neurocrine Collaboration Agreement for the FA Program, Neurocrine has agreed to fund the development through the Phase 1 clinical trial of VY- FXN01. After the achievement of milestones or metrics specified in the applicable development plan, as determined by the JSC, we have the option to either: (1) co- commercialize VY- FXN01 with Neurocrine in the United States under a 60 / 40 cost and profit- sharing arrangement, 60 % to Neurocrine and 40 % to us, or (2) retain the right to receive milestone payments and royalties based on global sales pursuant to the full global commercial rights granted to Neurocrine. Under the 2023 Neurocrine Collaboration Agreement, Neurocrine agreed to fund the non- clinical development activities for the GBA1 Program. Upon our receipt of topline data from the first Phase 1 clinical trial for a product ~~89candidate --~~ **candidate** being

developed pursuant to the GBA1 Program, we will have the option to either: (1) co- commercialize collaboration products in the GBA1 Program with Neurocrine in the United States under a 50 / 50 cost- and profit- sharing arrangement and receive milestones and royalties based on ex- U. S. sales, or (2) retain the right to receive milestone payments and royalties based on global sales pursuant to the full global commercial rights granted to Neurocrine. In the event we exercise our 2023 Co- Co Option, the parties have also agreed that Neurocrine is entitled to receive (in addition to its 50 % share of profits) 50 % of our share of profits until our obligation to repay 50 % of all development costs incurred by Neurocrine in connection with the GBA1 Program prior to such exercise have been paid off out of ~~such~~ **our** 50 % ~~of our~~ share of profits. The 2023 Co- Co Trigger Event is the date on which we receive topline data from the first Phase 1 clinical trial **in Parkinson' s disease** for a product candidate being developed pursuant to the GBA1 Program ~~. Under the 2023 Novartis Collaboration Agreement, Novartis is solely responsible for, and has sole decision- making authority with respect to, at its own expense, the exploitation of a product or product candidate under the Novartis SMA Program, or the Novartis SMA Program Product. With respect to the Novartis HD Program, the parties have agreed to conduct research and pre- clinical development of Novartis HD Program Products pursuant to a research plan, with Novartis reimbursing us for our activities thereunder in accordance with the agreed- to budget. From and after the first IND application filing for the Novartis HD Program, the parties have agreed that Novartis will assume sole responsibility for the development and commercialization of Novartis HD Program Products, including all further preclinical and clinical development and any commercialization of the Novartis HD Program products and product candidates. With respect to each of the Novartis SMA Program Products and Novartis HD Program Products, Novartis is obligated to use commercially reasonable efforts to develop and obtain regulatory approval for at least one of each such product in the United States and in certain other international markets specified in the 2023 Novartis Collaboration Agreement~~ . In the future, we may seek to enter into collaborations regarding other of our product candidates with other entities to utilize their established marketing and distribution capabilities, but we may be unable to enter into such agreements on favorable terms, if at all. If any current or future collaborators do not commit sufficient resources to commercialize our products, or we are unable to develop the necessary capabilities on our own, we will be unable to generate sufficient product revenue to sustain our business. We compete with many companies that currently have extensive, experienced and well- funded medical affairs, marketing and sales operations to recruit, hire, train and retain marketing and sales personnel. We also face competition in our search for third parties to assist us with the sales and marketing efforts of our product candidates. We might face unforeseen costs and expenses associated with creating an independent sales and marketing organization. Our sales personnel might also face difficulties obtaining access to physicians or being able to persuade adequate numbers of physicians to use or prescribe our products or selling our products if we lack complementary products, which could disadvantage us compared to companies with more extensive product lines. Without an internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies. ~~Our~~ **93Our** efforts to educate the medical community and third- party payors on the benefits of our product candidates may require significant resources and may never be successful. Such efforts may require more resources than are typically required due to the complexity and uniqueness of certain of our potential products. If any of our product candidates is approved but fails to achieve market acceptance among physicians, patients, or third- party payors, we will not be able to generate significant revenues from such product, which could harm our business, financial condition, results of operations and prospects. The insurance coverage and reimbursement status of newly- approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for our product candidates, if approved, could limit our ability to market those products and decrease our ability to generate product revenue. We expect the cost of a single administration of gene therapy products, such as those we are developing, to be substantial, when and if they receive regulatory approval. We expect that coverage and reimbursement by government and private payors will be essential for most patients to be able to afford these treatments. Accordingly, sales of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or will be reimbursed by government authorities, private health coverage insurers and other ~~90third~~ -- **third** - party payors. Coverage and reimbursement by a third- party payor may depend upon several factors, including the third- party payor' s determination that use of a product is: ● a covered benefit under its health plan; ● safe, effective and medically necessary; ● appropriate for the specific patient and the indication; ● convenient and easy- to- administer compared to alternative treatments; ● cost- effective compared to alternative treatments; and ● neither experimental nor investigational. No uniform policy requirement for coverage and reimbursement for biopharmaceutical products exists among third- party payors. Therefore, coverage and reimbursement for such products can differ significantly from payor to payor. As a result, obtaining coverage and reimbursement for a product from third- party payors is a time- consuming and costly process that could require us to provide to each different payor supporting scientific, clinical and cost- effectiveness data, and to receive the support of medical associations and technology assessment committees. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. If coverage and reimbursement are not available, or are available only at limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be adequate to realize a sufficient return on our investment including our research, development, manufacture, sales, and distribution expenses. Interim reimbursement levels for new drugs, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the drug and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost drugs and may be incorporated into existing payments for other services. Assuming we obtain coverage for a given product by a third- party payor, the resulting reimbursement payment rates may not be adequate or may require co- payments that patients find unacceptably high. Patients who are prescribed medications for the treatment of their conditions, and their prescribing physicians, generally rely on third- party payors to reimburse all or part of the costs associated with their prescription drugs. Patients are unlikely to use our products unless coverage is provided **,**

and reimbursement is adequate to cover all or a significant portion of the cost of our products. Therefore, coverage and adequate reimbursement are critical to new product acceptance. Additionally, there may be significant delays in obtaining coverage and reimbursement for newly approved drugs and biologics, and coverage may be more limited than the purposes for which the drug is approved by the FDA or comparable foreign regulatory authorities. ~~There~~ **94There** is significant uncertainty related to third- party coverage and reimbursement of newly approved products. In the United States, third- party payors, including government payors such as the Medicare and Medicaid programs, play an important role in determining the extent to which new drugs and biologics will be covered and reimbursed. The Medicare and Medicaid programs increasingly are used as models for how private payors and government payors develop their coverage and reimbursement policies. A primary trend in the U. S. healthcare industry and elsewhere is cost containment. Government authorities and third- party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. 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. The CMS is responsible for determining whether a product should be approved for coverage and reimbursement under the Medicare program. It is difficult to predict what CMS will decide with respect to coverage and reimbursement for novel products such as ours, as there is no body of established practices and precedents for these types of products. Currently, no gene therapy product has been approved for coverage and reimbursement by the CMS. Moreover, reimbursement agencies in the European Union may be more conservative than CMS. For example, several cancer drugs have been approved for reimbursement in the United States and have not been approved for reimbursement in certain European Union Member States. It is difficult to predict what third- party payors will decide with respect to the coverage ~~91and~~ -- **and** reimbursement for our product candidates, especially given that the cost of our product candidates is likely to be very high and pricing of such products is highly uncertain. Outside the United States, international operations generally are subject to extensive government price controls and other market regulations ~~,~~ and increasing emphasis on cost- containment initiatives in the European Union, Canada and other countries may put pricing pressure on us. In many countries, the prices of medical products are subject to varying price control mechanisms as part of national health systems. In general, the prices of medicines under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for medical products ~~,~~ but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable product revenues. Moreover, increasing efforts by government and third- party payors in the United States and abroad to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for our product candidates. Payors increasingly are considering new metrics as the basis for reimbursement rates, such as average sales price, or ASP, average manufacturer price, or AMP, and Actual Acquisition Cost. The existing data for reimbursement based on some of these metrics is relatively limited, although certain states have begun to survey acquisition cost data for the purpose of setting Medicaid reimbursement rates, and CMS has begun making pharmacy National Average Drug Acquisition Cost and National Average Retail Price data publicly available on at least a monthly basis. The regulations that govern marketing approvals, pricing, coverage and reimbursement for new drug and device products vary widely from country to country. Current and future legislation may significantly change the approval requirements in ways that could involve additional costs and cause delays in obtaining approvals. Some countries require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then be subject to price regulations that delay our commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenues we are able to generate from the sale of the product in that country. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost- effectiveness of our product candidate to other available therapies. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if our product candidates obtain marketing approval. Therefore, it is difficult to project the impact of these evolving reimbursement metrics on the willingness of payors to cover candidate products that we or our partners are able to commercialize. We expect to experience pricing pressures in connection with the sale of any of our product candidates due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on ~~healthcare~~ **95healthcare** costs in general, particularly prescription drugs and surgical procedures and other treatments, has become intense. As a result, increasingly high barriers are being erected to the entry of new products such as ours. The commercial success of any of our product candidates will depend upon its degree of market acceptance by physicians, patients, third- party payors and others in the medical community. Ethical, social and legal concerns about gene therapy could result in additional regulations restricting or prohibiting our gene therapy products. Even with the requisite approvals from the FDA in the United States, EMA in the European Union and other regulatory authorities internationally, the commercial success of our product candidates will depend, in part, on the support and acceptance of medical associations and technology assessment committees, physicians, patients and health care payors of proprietary antibody and gene therapy products in general, and our product candidates in particular, as medically necessary, cost- effective and safe. Any product that we commercialize may not gain acceptance by physicians, patients, health care payors and others in the medical community. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become ~~92profitable~~ -- **profitable** . The degree of market acceptance of proprietary antibody and gene therapy products and, in particular, our product candidates, if approved for commercial sale, will depend on several factors, including: ● the efficacy and safety of such product candidates as demonstrated in clinical trials; ● the potential and perceived advantages of product candidates over alternative

treatments; ● the cost of treatment relative to alternative treatments; ● the clinical indications for which the product candidate is approved by the FDA or the European Commission, or other regulatory authorities; ● patient awareness of, and willingness to seek, genotyping; ● the willingness of physicians to prescribe new therapies; ● the willingness of physicians to undergo specialized training with respect to administration of our product candidates; ● the willingness of the target patient population to try new therapies; ● the prevalence and severity of any side effects; ● product labeling or product insert requirements of the FDA, EMA or other regulatory authorities, including any limitations or warnings contained in a product' s approved labeling or restrictions on the use of our products together with other medications; ● relative convenience and ease of administration; ● the strength of marketing and distribution support; ● the timing of market introduction of competitive products; ● publicity concerning our products or competing products and treatments; and ● sufficient third- party payor coverage and reimbursement. ~~Even~~ **96Even** if a potential product displays a favorable efficacy and safety profile in preclinical studies and clinical trials, market acceptance of the product will not be fully known until after it is launched. Our gene therapy and vectorized antibody approaches utilize vectors derived from viruses that are selectively engineered, which may be perceived as unsafe or may result in unforeseen adverse events. Negative public opinion and increased regulatory scrutiny of gene therapy may damage public perception of the safety of our gene therapy product candidates and adversely affect our ability to conduct our business or obtain regulatory approvals for our gene therapy product candidates. Gene and vectorized antibody therapies remain novel technologies, with few gene therapy products approved to date in the United States and the European Union. Public perception may be influenced by claims that gene therapy is unsafe, and gene therapy may not gain the acceptance of the public or the medical community. Medical events such as the recent COVID- 19 pandemic that emphasize harmful effects of certain viruses could also indirectly foster negative public perception of virus- based therapies. In particular, our success will depend upon physicians who specialize in the treatment of genetic diseases targeted by our product candidates, prescribing treatments that involve the use of our ~~93product~~ -- **product** candidates in lieu of, or in addition to, existing treatments with which they are familiar and for which greater clinical data may be available. More restrictive government regulations or negative public opinion would have an adverse effect on our business, financial condition, results of operations and prospects and may delay or impair the development and commercialization of our product candidates or demand for any products we may develop. For example, earlier gene therapy trials led to several well- publicized adverse events, including cases of leukemia and death seen in other trials using non- AAV gene therapy vectors. Adverse events and SAEs in our clinical trials such as the MRI abnormalities detected in some patients dosed in the RESTORE- 1 Phase 2 clinical trial, or other clinical trials involving gene therapy products or our competitors' products, even if not ultimately attributable to the relevant product candidates, and the resulting publicity, could result in increased government regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates. If we obtain approval to commercialize our product candidates outside of the United States, in particular in the United Kingdom or European Union, a variety of risks associated with international operations could harm our business. We expect that we will be subject to additional risks in commercializing our product candidates outside the United States, including: ● different regulatory requirements for approval of drugs and biologics in foreign countries; ● reduced or loss of protection under our intellectual property rights; ● unexpected changes in tariffs, trade barriers and regulatory requirements; ● economic weakness, including inflation, or political instability in particular foreign economies and markets; ● compliance with tax, employment, immigration and labor laws for employees living or traveling abroad; ● foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country; ● workforce uncertainty in countries where labor unrest is more common than in the United States; ● shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; **97** ● business interruptions resulting from geopolitical actions, including war and terrorism, from natural disasters including earthquakes, typhoons, floods and fires, or from economic, social, or political instability; and ● greater difficulty with enforcing our contracts in jurisdictions outside of the United States. We must dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we plan to operate. The creation, implementation and maintenance of international business practices compliance programs is costly and such programs are difficult to enforce, particularly where reliance on third parties is required. The Foreign Corrupt Practices Act, or FCPA, prohibits any U. S. individual or business from paying, offering, authorizing payment or offering anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of the foreign entity in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with certain accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the corporation, including international subsidiaries, and to devise and maintain an adequate system of ~~94internal~~ -- **internal** accounting controls for international operations. The anti- bribery provisions of the FCPA are enforced primarily by the Department of Justice. The SEC is involved with enforcement of the books and records provisions of the FCPA. Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. In many foreign countries, it is common for others to engage in business practices that are prohibited by U. S. laws and regulations applicable to us, including the FCPA. In addition, the FCPA presents particular challenges in the pharmaceutical industry because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials. Certain payments to hospitals in connection with clinical trials and other work have been deemed to be improper payments to government officials and have led to FCPA enforcement actions. Various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non- U. S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. If we expand our presence outside of the United States, we will be required to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing, or selling certain products and product candidates outside of the United States,

which could limit our growth potential and increase our development costs. The failure to comply with laws governing international business practices may result in substantial civil and criminal penalties and suspension or debarment from government contracting. The SEC also may suspend or bar issuers from trading securities on U. S. exchanges for violations of the FCPA' s accounting provisions. Although we expect to implement policies and procedures designed to comply with these laws and policies, there can be no assurance that our employees, contractors and agents will comply with these laws and policies. If we are unable to successfully manage the challenges of international expansion and operations, our business and operating results could be harmed. Risks Related to Our Intellectual PropertyOur rights to develop and commercialize our product candidates are subject to, in part, the terms and conditions of licenses granted to us by others. We are reliant upon licenses to certain patent rights and proprietary technology from third parties that are important or necessary to the development of our technology and products, including technology related to our manufacturing process and our product candidates. These and other licenses may not provide exclusive rights to use such intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology and products in the future. As a result, we may not be able to prevent competitors from developing and commercializing competitive products in territories included in all of our licenses. These licenses may also require us to grant back certain rights to licensors and / or to pay certain amounts relating to the use of the licensed intellectual property. For example, the Touchlight License Agreement obligates us to make future milestone and royalty ~~payments~~ **98payments** if we, or our collaboration partners or TRACER Capsid licensees, use a capsid created using certain DNA preparation processes licensed under the Touchlight License Agreement. In some circumstances, particularly in- licenses with academic institutions, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain, enforce or defend the patents, covering technology that we license from third parties. Therefore, we cannot be certain that these patents and applications will be prosecuted, maintained and enforced in a manner consistent with the best interests of our business. If our licensors fail to maintain such patents, or lose rights to those patents or patent applications, the rights we have licensed may be reduced or eliminated and our right to develop and commercialize any of our products that are the subject of such licensed rights could be adversely affected. In certain circumstances, we have or may license technology from third parties on a non- exclusive basis. In such instances, other licensees may have the right to enforce our licensed patents in their respective fields, without our oversight or control. Those other licensees may choose to enforce our licensed patents in a way that harms our interest, for example, by advocating for claim interpretations or agreeing on invalidity positions that conflict with our positions or our interest. In addition to the foregoing, the risks associated with patent rights that we license from third parties will also apply to patent rights we own or may own in the future. ~~95Further~~ -- **Further** , in many of our license agreements we are responsible for bringing any actions against any third party for infringing on the patents we have licensed. Certain of our license agreements also require us to meet development thresholds to maintain the license, including establishing a set timeline for developing and commercializing products and minimum yearly diligence obligations in developing and commercializing the product. Certain of our license agreements contain " no challenge " clauses which preclude and prevent us from taking any action to limit or narrow the intellectual property of a licensor. In some cases, these limitations extend to any intellectual property of our licensor and not just that which is licensed to us. Such constraints may limit our ability to develop or commercialize products or to expand such efforts beyond the scope of any license. Disputes may arise regarding intellectual property subject to a licensing agreement, including: ● the scope of rights granted under the license agreement and other interpretation- related issues; ● the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement; ● the sublicensing of patent and other rights under our collaborative development relationships; ● our diligence obligations under the license agreement and what activities satisfy those diligence obligations; ● the inventorship or ownership of inventions and know- how resulting from the creation or use of intellectual property by our licensors and us and our partners; and ● the priority of invention of patented technology. 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 product candidates. If we fail to comply with our obligations under these license agreements, or we are subject to a bankruptcy, the licensor may have the right to terminate the license, in which event we would not be able to develop, manufacture, or market products covered by the license or may face other penalties under the agreements. Termination of any of our agreements involving intellectual property or reduction or elimination of our rights under these agreements may result in our having to negotiate new or reinstated agreements with less favorable terms or cause us to lose our rights under these agreements, including our rights to important intellectual property or technology. Termination may also result in unfavorable terms associated with such termination or may result in obligations on our part to license or grant back intellectual property rights to prior licensors. ~~Furthermore~~ **99Furthermore** , the research resulting in certain of our licensed patent rights and technology was funded by the U. S. government. As a result, the government may have certain rights, or march- in rights, to such patent rights and technology. When new technologies are developed with U. S. government funding, the U. S. government generally obtains certain rights in any resulting patents, including a non- exclusive, royalty- free license authorizing the U. S. government, or a third party on its behalf, to use the invention for non- commercial purposes. These rights may permit the government to disclose our confidential information to third parties and to exercise march- in rights to use or allow third parties to use our licensed technology. The U. S. government can exercise its march- in rights if it determines that action is necessary because we fail to achieve practical application of the government- funded technology, because action is necessary to alleviate health or safety needs, to meet requirements of federal regulations or to give preference to U. S. industry. In addition, our rights in such inventions may be subject to certain requirements to manufacture products embodying such inventions in the United States. Any exercise by the government, or a third party on its behalf, of such rights could harm our competitive position, business, financial condition, results of operations and prospects. ~~96If~~ **If** we are unable to obtain and maintain patent protection for our products and technology, 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 products and technology may be adversely affected. Our success depends, in large part, on our and our licensors' ability to obtain and maintain patent protection in the United States and other countries with respect to our product candidates and manufacturing technology. We and our licensors have sought, and we intend to seek in the future, to protect our proprietary position by filing patent applications in the United States and abroad related to many of our technologies and product candidates that are important to our business. The patent prosecution process is expensive, time- consuming and complex, and we may not have and may not in the future be able to file, prosecute, maintain, enforce, defend or license all necessary or desirable patent applications in some or all relevant jurisdictions at a reasonable cost or in a timely manner. For example, in some cases, the work of certain academic researchers and biotechnology and biopharmaceutical companies in the gene therapy **and non- viral therapeutic** ~~field~~ **fields** has entered the public domain, which may compromise our ability to obtain patent protection for certain inventions related to or building upon such prior work. Consequently, we may not be able to obtain any such patents to prevent others from using our technology for, and developing and marketing competing products to treat, these indications. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. In some cases, we may be able to obtain patent protection, but such protections may expire before we commercialize the product protected by those rights, leaving us no meaningful protection for our products. In other cases, where our intellectual property is being managed by a third- party collaborator, licensee or partner, that third party may fail to act diligently in prosecuting, maintaining, defending or enforcing our patents. Such conduct may result in the failure to maintain or obtain protections, loss of rights, loss of patent term or, in cases where a third party has acted negligently or inequitably, patents being found unenforceable. The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions and has, in recent years, been the subject of much litigation. As a result, the issuance, scope, validity, enforceability and commercial value of our and our licensors' patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which protect our technology or product candidates or which effectively prevent others from commercializing competitive technologies and product candidates. In particular, during prosecution of any patent application, the issuance of any patents based on the application may depend upon our ability to generate additional preclinical or clinical data that support the patentability of our proposed claims. We may not be able to generate sufficient additional data on a timely basis, or at all. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish the value, narrow the scope, or eliminate the enforceability of our and our licensors' patent protection. We may not be aware of all third- party intellectual property rights potentially relating to our product candidates, particularly due to the competitive and rapidly- evolving gene therapy **and non- viral therapeutic** patent landscape. 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, only ~~upon~~ **100upon** issuance or not at all. Therefore, we cannot be certain that we, or a licensor, were the first to make the inventions claimed in any owned or any licensed patents or pending patent applications, respectively, or which entity was the first to file for patent protection until such patent application publishes or issues as a patent. Databases for patents and publications, and methods for searching them, are inherently limited, so it is not practical to review and know the full scope of all issued and pending patent applications. As a result, the issuance, scope, validity, enforceability, and commercial value of our and our licensed patent rights are uncertain. Even if the patent applications we license or may own in the future do 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. Our competitors or other third parties may be able to circumvent our patents by developing similar or alternative technologies or products in a non- infringing manner. ~~97In~~ **In** spite of a legal presumption of validity, the issuance of a patent is not conclusive as to its inventorship, ownership, scope, validity, or enforceability which may be challenged in the courts and patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and product candidates. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such 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. Our intellectual property licenses with third parties may be subject to disagreements over contract interpretation, which could ~~narrow~~ **impact** the scope of our rights to the relevant intellectual property or technology, ~~resulting~~ --- **result in delays and increased costs associated with the resolution of the disagreements, result** in termination of our access to such intellectual property, or increase our financial or other obligations to our licensors **, licensees, or collaborators** . The agreements under which we currently **in-** license intellectual property or technology from **, or out- license our intellectual property to,** third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could ~~narrow~~ **result in delays and costs associated with the resolution of such disagreement, impact** what we believe to be the scope of our **or the third party' s** rights to the relevant intellectual property or technology, result in loss of access **to a license or other rights that are necessary for developing, commercializing and protecting our platform technologies and products, result in allegations that we have failed to comply with our obligations under any licenses or related agreements** , or increase what we believe to be our financial or other obligations under the relevant agreement, any of which could harm our business, financial condition, results of operations and prospects. We may not be successful in obtaining necessary rights to our product candidates through acquisitions and in- licenses. We currently have rights to certain intellectual property, through licenses from third parties, to develop our product candidates. Because our programs may require the use of proprietary rights held by third parties, the growth of our business likely will depend, in part, on our ability to acquire, in- license

or use these proprietary rights. We may be unable to 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 product candidates. 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. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical or technical 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. We currently co- own certain intellectual property rights with one or more third parties. We may not be able to obtain a license to the third parties' interest such that we have exclusive access and control of such co- owned assets. In ~~this~~ **101this** case, and depending on the jurisdiction of the patent filing, we may not be able to license, enforce, or exploit the co- owned rights without the consent from, or an accounting to, the other co- owners. We sometimes collaborate with non- profit and academic institutions to accelerate our preclinical research or development under written agreements with these institutions. Typically, these institutions provide us with an option to negotiate a license to any of the institution' s rights in technology resulting from the collaboration. Regardless of such option, we may be unable to negotiate a license 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 other parties, potentially blocking our ability to develop our program. We may also decide not to exercise an option to such institutional rights. If we decide not to obtain, or are unable to successfully obtain rights to required third- party intellectual property rights or maintain the existing intellectual property rights we have, we may be required to expend significant time and resources to redesign our product candidates or the methods for manufacturing them or to develop or license replacement technology, all of which may not be feasible on a technical or commercial basis. If we are unable to do so, we may be unable to develop or commercialize the affected product candidates, which could harm our business significantly. ~~98Obtaining~~ -- **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 / or applications will be due to be paid to the United States Patent and Trademark Office, or USPTO, and various government patent agencies outside of the United States over the lifetime of our licensed patents and / or applications and any patent rights we may own in the future. We rely on our outside counsel or our licensors to pay these fees due to patent agencies. The USPTO and various non- U. S. government patent agencies require compliance with several procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply and 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 many 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 partial or complete loss of patent rights in the relevant jurisdiction, and may compromise the strength of other intellectual property in our portfolio. In such an event, potential competitors might be able to enter the market **,** and this circumstance could harm our business ~~. On February 1, 2019 the government of Venezuela, in response to certain U. S. sanctions, began to require that foreign entities pay all official fees, including patent fees (either for pending matters or new petitions), in PETRO, a " cryptocurrency " created by the Nicolás Maduro administration in February 2018 as a way to collect U. S. dollars while avoiding American financial sanctions issued under an Executive Order of President Trump on March 19, 2018. The Executive Order banned transactions involving " any digital currency, digital coin, or digital token, that was issued by, for, or on behalf of the Government of Venezuela on or after January 9, 2018. " The prohibition is applicable to any U. S. entity unless exempted by license. We do not hold such a license and therefore may not be able to secure patents in Venezuela~~ . We may not be able to protect our intellectual property rights throughout the world. Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive. Our intellectual property rights may vary from country to country and foreign protections could be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing. Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology products or methods of treatment, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. For example, an April ~~2023~~ **2024** report from the Office of the United States Trade Representative identified a number of countries, including India and China, where challenges to the procurement and enforcement of patent rights have been reported. Several countries, ~~including~~ **102including** India and China, have been listed in the report every year since 1989. ~~With~~ **Following** Brexit, there ~~is uncertainty~~ **have been changes** associated with obtaining, defending, and enforcing intellectual property rights in the United Kingdom **, including requirements** ~~. International treaties and regulations promulgated as a result of this transition could impede or~~ **for** ~~eliminate our ability~~ **separate filings and registrations in the United Kingdom that may lead** to **increased costs and risks associated with** ~~obtain~~ **obtaining** or ~~maintain~~ **maintaining** ~~meaningful~~ intellectual property

rights in the United Kingdom. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we ~~99initiate~~ **initiate**, and 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. Issued patents covering our technology or product candidates could be found invalid or unenforceable if challenged in court. We may not be able to protect our trade secrets in court. If one of our licensees or licensors or we initiate legal proceedings against a third party to enforce a patent covering our technology or one of our product candidates, the defendant could counterclaim that the patent covering such technology or product candidate 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 subject matter eligibility, lack of novelty, obviousness, lack of written description, failure to enable third parties to practice the relevant invention, or **double patenting, in particular, obviousness- type double patenting, which if successful, could result in a finding that the claims are invalid or the loss of patent term, including a patent term adjustment granted by the USPTO, if a terminal disclaimer is filed to obviate a finding of obviousness- type** double patenting. Grounds for an unenforceability assertion could be an allegation that an individual connected with prosecution of the patent, including an inventor, an employee of the company, a collaborator or advisor, 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 pre- issuance submissions, ex parte re- examination, post- grant review, inter partes review and equivalent proceedings in foreign jurisdictions. Some of these mechanisms may even be exploited anonymously by third parties. Such proceedings could result in the revocation or cancellation of or amendment to our patents in such a way that they no longer cover our technology or product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which the patent examiner and we or our licensees or licensors were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we could lose part or, all of the patent protection on one or more of our product candidates or our supporting technology. Such a loss of patent protection could harm our business. In addition to the protection afforded by patents, we rely on trade secret protection, nondisclosure, and confidentiality agreements to protect proprietary know- how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know- how, information or technology that is not covered by patents. However, trade secrets can be difficult to protect. Some courts inside and outside the United States are less willing or unwilling to protect trade secrets. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors, collaborators, contractors, and other third parties. 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. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. ~~Third~~ **103Third** parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain and could harm our business. Our commercial success depends upon our ability and the ability of our collaborators to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights and intellectual property of third parties. The biotechnology and pharmaceutical industries are characterized by extensive and complex litigation regarding patents and other intellectual property rights. We may become party to, or threatened with, infringement litigation claims regarding our products and technology, including claims from competitors or from non- practicing entities that have no relevant product revenue and against whom our own patent portfolio may have no deterrent effect. Moreover, we may become party to, or be threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our product candidates and technology, including ex parte re- examination, post- grant review and inter partes review before the USPTO or foreign patent offices. Third parties may ~~100assert~~ **assert** infringement claims against us based on existing patents or patents that may be granted in the future, regardless of the merit of the claim. In November 2022, we and Touchlight entered into the Touchlight License Agreement to allow for our historical use of a certain DNA preparation process, or the Subject DNA Preparation Process, and to authorize the prospective exploitation of TRACER Capsids that we have previously created using the Subject DNA Preparation Process. ~~As previously referenced in the Risk Factor section of our prior periodic reports,~~ Touchlight had made us aware in early 2022 that it believed that some of its intellectual property rights could potentially be asserted against us, although we disagreed with this assessment. In connection with entering into the Touchlight License Agreement, Touchlight also agreed to release any potential claims against us regarding the alleged historical use of certain of Touchlight' s intellectual property rights and exploitation of TRACER Capsids created with the alleged use of such intellectual property rights. Potential parties may emerge and choose to engage in litigation with us to enforce or to otherwise assert their patent rights against us. Even if we believe such claims are without merit, a court of competent jurisdiction could hold that these third- party patents are valid, enforceable and infringed, which could adversely affect our ability to commercialize our product candidates or any other of our product candidates or technologies covered by the asserted third- party patents. In order to successfully challenge the validity of any such asserted third- party U. S. patent in federal court, we would need to overcome a presumption of validity. As this burden is a high one

requiring us to present clear and convincing evidence as to the invalidity of any such U. S. patent claim, there is no assurance that a court of competent jurisdiction would invalidate the claims of any such U. S. patent. Similar challenges exist in other jurisdictions. If we are found to infringe a third- party' s valid and enforceable intellectual property rights, we could be required to obtain a license from such third- party to continue developing, manufacturing and marketing our product candidates and technology. 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 a license, it could be non- exclusive, thereby giving our competitors and other third parties access to the same technologies licensed to us, and it could require us to make substantial licensing and royalty payments. We could be forced, including by court order, to cease developing, manufacturing and commercializing the infringing technology or product candidates. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent or other intellectual property ~~right~~ **rights** . A finding of infringement could prevent us from manufacturing and commercializing our product candidates or force us to cease some of our business operations, which could harm our business. In addition, we may be forced to redesign our product candidates, seek new regulatory approvals, and indemnify third parties pursuant to contractual agreements. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business, reputation, financial condition, results of operations and prospects. Intellectual property litigation could cause us to spend substantial resources and distract our personnel from their normal responsibilities. Competitors may infringe our intellectual property rights or the intellectual property rights of our licensees or licensors, or we may be required to defend against claims of infringement. To counter infringement or unauthorized use claims or to defend against claims of infringement can be expensive and time- consuming. 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 technical and management personnel from their normal responsibilities. In addition, there could be ~~public~~ **104public** announcements of the results of hearings, motions or other interim proceedings or developments. 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 adversely affect our ability to compete in the marketplace. ~~101We~~ **We** may be subject to claims asserting that our employees, consultants or advisors have wrongfully used or disclosed alleged trade secrets or other proprietary confidential information or know- how of their current or former employers or claims asserting ownership of what we regard as our own intellectual property. Many of our directors, 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 these individuals do not use the proprietary information or know- how of others in their work for us, we may be subject to claims that these individuals or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual' s current or former employer. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management. In addition, while it is our policy to require our employees, consultants, advisors 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. If we fail in prosecuting or 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 prosecuting or defending against such claims, litigation could result in substantial costs and be a distraction to management. Changes in U. S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products. Patent reform legislation could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. On September 16, 2011, the Leahy- Smith America Invents Act, or the Leahy- Smith Act, was signed into law. The Leahy- Smith Act includes several significant changes to U. S. patent law. These include provisions that affect the way patent applications are prosecuted and also may affect patent litigation. These also include provisions that switched the United States from a " first- to- invent " system to a " first- inventor- to- file " system, allow third- party submission of prior art to the USPTO during patent prosecution and set forth additional procedures to attack the validity of a patent by the USPTO administered post grant proceedings. Under a first- inventor- to- file system, assuming the other requirements for patentability are met, the first inventor to file a patent application generally will be entitled to the patent on an invention regardless of whether another inventor had made the invention earlier. The USPTO has promulgated regulations and procedures to govern administration of the Leahy- Smith Act, and many of the substantive changes to patent law associated with the Leahy- Smith Act, and in particular, the first- inventor- to- file provisions, became effective on March 16, 2013. The Leahy- Smith Act has resulted in increased pressure to invest in filing applications earlier, and consequently has increased the uncertainties and costs surrounding the prosecution of our patent applications, and may increase the enforcement or defense of our issued patents, all of which could harm our business, financial condition, results of operations and prospects. ~~The~~ **105The** administrative tribunal created by the Leahy- Smith Act, known as the Patent Trial and Appeals Board, or PTAB, may have an impact on the operation of our business in the future. For example, the initial results of patent challenge proceedings before the PTAB since its inception in 2013 have resulted

in the invalidation of many U. S. patent claims. The availability of the PTAB as a lower- cost, faster and potentially more potent tribunal for challenging patents could therefore increase the likelihood that our ~~own~~ **owned or** licensed patents will be challenged, thereby increasing the uncertainties and costs of maintaining and enforcing them. Moreover, if such challenges occur, we may not have the right to control the defense. In certain situations, we may be required to rely on our licensor to consider our suggestions and to defend such challenges, with the possibility that it may not do so in a way that best protects our interests. ~~102We~~ **We** also may be subject to a third- party pre- issuance submission of prior art to the USPTO or become involved in other contested proceedings such as opposition, derivation, reexamination, inter partes review, or post- grant review proceedings challenging our patent rights or the patent rights of others. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products 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. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future products. The patent positions of companies engaged 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. For example, the Supreme Court of the United States held in Amgen v. Sanofi (May 18, 2023) that a functionally claimed genus** ~~as~~ **was invalid for failing to comply with** the **enablement requirement of the Patent Act of 1952. In addition, the Federal Circuit has recently issued several decisions involving the interaction of patent term adjustment, terminal disclaimers, and obviousness- type double patenting (Allergan USA, Inc. v. MSN Laboratory Private Ltd. (August 13, 2024); In re: Cellect. LLC (August 28, 2023)). The** courts **have also** ~~address~~ **addressed** issues ~~such as~~ **pertaining to** patenting genes or gene products. ~~Recent guidance~~ **Guidance** provided under Berkheimer v HP, Inc. (April 19, 2018) and Vanda Pharmaceuticals, Inc. v West- Ward Pharmaceuticals (June 7, 2018) instruct USPTO examiners on the ramifications of the court rulings as applied to method of treatment claims, natural products and principles including all naturally occurring nucleic acids. Patents for certain of our product candidates contain claims related to specific DNA sequences that are naturally occurring and, therefore, could be the subject of future challenges made by third parties. In addition, the recent USPTO guidance could make it impossible for us to pursue similar patent claims in patent applications we may prosecute in the future. We cannot assure you that our efforts to seek patent protection for our technology and products will not be negatively impacted by the court decisions referenced above, rulings in other cases or changes in guidance or procedures issued by the USPTO. We cannot fully predict what impact decisions from the U. S. Supreme Court' s decisions in Mayo Collaborative Services v. Prometheus Laboratories and Molecular Pathology v. Myriad Genetics, Inc. or other applicable court decisions may have on the ability of life science companies to obtain or enforce patents relating to their products and technologies in the future. These decisions, the guidance issued by the USPTO and rulings in other cases or changes in USPTO guidance or procedures could have an adverse effect on our existing patent portfolio and our ability to protect and enforce our intellectual property in the future. Moreover, although the U. S. Supreme Court has held that isolated segments of naturally occurring DNA are not patent-eligible subject matter, certain third parties could allege that activities that we may undertake infringe other gene- related patent claims, and we may deem it necessary to defend ourselves against these claims by asserting non- infringement and / or invalidity positions, or paying to obtain a license to these claims. In any of the foregoing or in other situations involving third- party intellectual property rights, if we are unsuccessful in defending against claims of patent infringement, we could be forced to pay damages or be subjected to an injunction that would prevent us from utilizing the patented subject matter. Such outcomes could harm our business, financial condition, results of operations or prospects. Outside the United States, other courts have also begun to address the patenting of genetic material. In August 2015, the Australian High Court ruled that isolated genes cannot be patented in Australia. The decision did not address methods of using genetic material. Any ruling of a similar scope in other countries could affect the scope of our ~~intellectual~~ **106intellectual** property rights. The ambiguities and changing law in all countries as to patenting genetic material may directly affect our ability to secure and / or maintain patent protection for our gene therapy products. If we do not obtain patent term extension and regulatory exclusivity for our product candidates, our business may be harmed. Patents have a limited lifespan. In the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U. S. non- provisional filing date. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired, we may be open to competition from competitive products, including generics or biosimilars. Depending upon the timing, duration and specifics of any FDA marketing approval of our product candidates, one or more of our U. S. patents, which may cover non- gene therapy compounds, may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch- Waxman Act. The ~~103Hatch~~ --- **Hatch** - Waxman Act permits 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 per FDA- approved product, and only those claims covering the approved drug, an approved method for using it, or a method for manufacturing it may be extended. Further, certain of our licenses currently or in the future may not provide us with the right to control decisions the licensor or its other licensees on Orange Book listings or patent term extension decisions under the Hatch- Waxman Act. Thus, if one of our important licensed patents is eligible for a patent term extension under the Hatch- Waxman Act, and it covers a product of another licensee in addition to our own product candidate, we may not be able to obtain that extension if the other licensee seeks and obtains that extension first. 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. The BPCIA provides up to 12 years of market exclusivity

for a reference biological product. We may not be able to obtain such exclusivity for our products. Moreover, the applicable time- period or the scope of patent protection afforded during any such extension could be less than we request. If we are unable to obtain patent term extension or the scope of term of any such extension is less than we request, the period during which we will have the right to exclusively market our product may be shortened and our competitors may obtain approval of competing products following our patent expiration, and our revenue could be materially reduced. 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 such rights may not adequately protect our business or permit us to maintain our competitive advantage. For example: ● others may be able to make antibody ~~or ,~~ gene therapy **, or non- viral therapeutic** products that are similar to our product candidates but that are not covered by the claims of the patents that we own, license or may access in the future; ● we, or our license partners or current or future collaborators, might not have been the first to make the inventions covered by the issued patent or pending patent application that we license or may own in the future; ● we, or our license partners or current or future collaborators, might not have been the first to file patent applications covering certain of our or their inventions; ● others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our owned or licensed intellectual property rights; **107** ● it is possible that our pending patent applications or those that we may own in the future will not lead to issued patents **, or result in issued patents with a scope of protection that could be designed around or circumvented by our competitors** ; ● issued patents that we hold rights to may be held invalid or unenforceable, including as a result of legal challenges by our competitors; ● our competitors 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 have an adverse effect on our business; ~~and104~~ **and** ● we may choose not to file a patent for certain inventions, trade secrets or know- how, and a third party may subsequently file a patent covering such intellectual property. Should any of these events occur, they could significantly harm our business, financial condition, results of operations and prospects. We may not be able to maintain sufficient control over our proprietary know- how or trade secrets when employees, consultants, advisors or persons with access to our proprietary information terminate their relationship with us. Despite our efforts to protect our proprietary know- how and trade secrets, our competitors may discover this information, or obtain the benefit of this information, through a breach of confidentiality and / or non-competition obligations by persons who were formerly associated with us but who have established relationships as employees, contractors, consultants or advisors with other companies, including our competitors. The recent departures of certain executives, key employees, consultants or advisors, and the restructuring of our organization, may make it more difficult to enforce our rights in protecting this information. Further, if discovered in a timely manner, our efforts to enforce rights to protect against these types of breaches may not be possible under law, or may not be successful if commenced. It is also possible that, as we grow and establish ourselves in multiple geographic areas, alignment and / or compliance with company ~~polices~~ **policies** may not be consistently maintained. In any such cases, the risk of loss of control or proper management of our proprietary information could jeopardize our intellectual property. Our reliance on third parties requires us to share our trade secrets, confidential information and know- how, which increases the possibility that a competitor will discover them or that our trade secrets, confidential information and / or know- how will be misappropriated or disclosed. Because we currently rely on certain third parties to manufacture all or part of our product candidates and to perform quality testing, and because we collaborate with various organizations and academic institutions for the advancement of our proprietary antibody program and gene therapy ~~and~~ **,** vectorized antibody **, and non- viral therapeutic** platforms and programs, 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 and know- how increases the risk that such trade secrets and confidential information and know- how become known by our competitors, are inadvertently incorporated into the technology of others **, are included in third- party patent or regulatory filings,** 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, a competitor' s discovery of our ~~proprietary~~ **108proprietary** 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. Despite our efforts to protect our trade secrets and know- how, our competitors may discover our trade secrets or know- how, either through breach of these agreements, independent development or publication of information including our trade secrets or know- how by third parties. A competitor' s discovery of our trade secrets and / or know- how would impair our competitive position and have an adverse impact on our business, financial condition, results of operations and prospects. Risks Related to Ownership of Our Common Stock Sales of a substantial number of shares of our common stock in the public market could cause our stock price to fall. Persons who were our stockholders prior to our initial public offering continue to hold a substantial number of shares of our common stock. If such persons sell, or indicate an intention to sell, substantial amounts of our common stock in the public market, the trading price of our common stock could decline. ~~105In~~ **In** January 2024, we completed a private placement of 2, 145, 002 shares of our common stock to Novartis and an underwritten public offering of 7, 777, 778 shares of our common stock and pre- funded warrants to purchase up to 3, 333, 333 shares of our common stock. In addition, shares of common stock that are either subject to outstanding options or restricted stock units, or RSUs, or reserved for future issuance under our stock incentive plans will become eligible for sale in the public market to the extent permitted by the provisions of various vesting schedules and Rule 144 and Rule 701 under the Securities Act of 1933, as amended. We have also filed registration statements

on Form S- 8 permitting shares of common stock issued on exercise of options or the settlement of RSUs to be freely sold in the public market. If these additional shares of common stock are sold, or if it is perceived that they will be sold, in the public market, the trading price of our common stock could decline. We also have an effective registration statement on Form S- 3 for the sale of up to $ 300. 0 million in aggregate of an indeterminate number of shares of common stock and preferred stock, an indeterminate principal amount of debt securities, and an indeterminate number of depositary shares, subscription rights, warrants, purchase contract and units, **pursuant to which we have issued and sold approximately $ 100. 0 million** of **securities in January 2024 and under** which we have reserved $ 75. 0 million for the offering, issuance, and sale of common stock through at- the- market offerings or negotiated transactions under a sales agreement we entered into with Cowen and Company, LLC, on November 8, 2022. Certain holders of our common stock have rights, subject to specified conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. Any sales of securities by these stockholders could have a material adverse effect on the trading price of our common stock. The price of our common stock may be volatile and fluctuate substantially, which could result in substantial losses for purchasers of our common stock. The price of our common stock is likely to be volatile and may fluctuate substantially. **For example,** ~~From~~ **from** January 1, ~~2023~~ **2024** through December 31, ~~2023~~ **2024** , the sales price of our common stock ranged from a high of $ ~~14~~ **10** . ~~34~~ **84** to a low of $ 5. ~~87~~ **19** on the Nasdaq Global Select Market. As a result of this volatility, our stockholders may not be able to sell their common stock at or above the price at which they purchased it. The market price for our common stock may be influenced by many factors, including: ● ~~our success in commercializing any product candidates for which we obtain marketing approval; ●~~ regulatory action and results of clinical trials of our product candidates or those of our competitors; ● the success of competitive products or technologies; ● the results of clinical trials of our product candidates; ● the results of clinical trials of product candidates of our competitors; **109** ● the commencement, termination, and success of our collaborations, including the ability or willingness of our collaboration partners to fulfill their obligations to us; ● regulatory or legal developments in the United States and other countries; ● developments or disputes concerning patent applications, issued patents or other proprietary rights; ● the recruitment or departure of key personnel; ● the level of expenses related to any of our product candidates or clinical development programs; ● the results of our efforts to discover, develop, acquire or in- license additional product candidates or technologies, the cost of commercializing such product candidates, and the cost of development of any such product candidates or technologies; ~~106~~ ● actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts; ● variations in our financial results or those of companies that are perceived to be similar to us **; ● our success in commercializing any product candidates for which we obtain marketing approval** ; ● the ability to secure third- party reimbursement for our product candidates; ● changes in the structure of healthcare payment systems; ● market conditions in the pharmaceutical and biotechnology sectors; ● general economic, industry and market conditions, including interest rates and inflation; and ● other factors described in this " Risk Factors " section and elsewhere in this Annual Report on Form 10- K. If our operating results fall below the expectations of investors or securities analysts for a given period, the price of our common stock could decline substantially. Furthermore, any fluctuations in our operating results from period to period may, in turn, cause the price of our stock to fluctuate substantially. We believe that such comparisons of our financial results are not necessarily meaningful and should not be relied upon as an indication of our future performance. In the past, following periods of volatility in the market price of a company' s securities, securities class- action litigation often has been instituted against that company. We also may face securities class- action litigation if we cannot obtain regulatory approvals for or if we otherwise fail to commercialize our product candidates. We and certain of our current and former officers and directors were previously named as defendants in a purported class action lawsuit. This proceeding and other similar litigation, if instituted against us, could cause us to incur substantial costs to defend such claims and divert management' s attention and resources, which could seriously harm our business, financial condition, results of operations and prospects. We ~~have broad discretion in how we apply our available funds, and we may not~~ **no longer qualify as** use these funds effectively, which could..... or that loses value. We are a " smaller reporting company " and **, commencing with our Quarterly Report on Form 10- Q for** the **quarter ending March 31, 2025, we may no longer take advantage of** reduced disclosure **and reporting** requirements applicable to ~~such~~ **smaller reporting** companies **, which will require us** ~~may make our common stock less attractive~~ to ~~investors~~ **incur significant expenses and expend time and resources** . We ~~are~~ **no longer qualify as** a " smaller reporting company ~~,~~ " as defined in Rule 12b- 2 under the Securities Exchange Act of 1934, as amended **, based on our** ~~. We would cease to qualify as a smaller reporting company if we have (a) a~~ non- affiliate public float in excess of $ 250 million and **our** annual revenues in excess of $ 100 million during our last fiscal year, ~~or (b) a non- affiliate public float in excess of $ 700 million,~~ in each case determined ~~on an annual basis~~ as of the last business day of our second quarter **of 2024** . As a smaller reporting company, we ~~are~~ **were** permitted and **relied** ~~intend to rely~~ on exemptions from certain disclosure ~~requirements~~ **110requirements** that are applicable to other public companies that are not smaller reporting companies. These exemptions ~~include~~ **included** : ● being permitted to provide only two years of audited consolidated financial statements in this Annual Report on Form 10- K, with correspondingly reduced " Management' s Discussion and Analysis of Financial Condition and Results of Operations " disclosure; ● reduced disclosure obligations regarding executive compensation; ~~and107~~ **and** ● not being required to furnish a stock performance graph in our annual report. We expect to continue to take advantage of some or all of the available exemptions ~~until we cease~~ **through the filing of this Annual Report on Form 10- K for the year ended December 31, 2024, and any portions of our definitive proxy statement relating** to **our 2025 Annual Meeting of Stockholders incorporated by reference herein. We cannot predict whether investors will find our common stock less attractive if we rely on these exemptions. If some investors find our common stock less attractive as a result, there may** be a ~~smaller reporting company. We~~ **less active trading market for our common stock and our stock price** may ~~cease~~ **be more volatile. Following the filing of this Annual Report and the definitive proxy statement relating** to **our** ~~qualify as a smaller reporting company as early as June 30, 2024~~ **2025 Annual Meeting of Stockholders** , ~~which would~~ **we will**

**be** ~~require~~ **required** ~~as~~ to comply with disclosure requirements that are applicable to other public companies that are not smaller reporting companies ~~following~~ **. Compliance with** ~~the~~ **these** ~~filing of~~ **additional requirements may increase** our ~~Annual Report on Form 10- K for~~ **legal and financial compliance costs and divert the attention of management and** ~~the~~ **other personnel from operational** ~~year ending December 31, 2024,~~ and **other business matters** ~~any portions of our definitive proxy statement relating~~ to ~~our 2025 Annual Meeting~~ **these additional public company reporting requirements. If we are not able to comply with changing requirements in a timely manner, the market price** of ~~Stockholders incorporated~~ **our stock could decline, and we could be subject to delisting proceedings** by ~~reference therein. We cannot predict whether investors will find our common stock less attractive if we rely on these~~ -- **the Nasdaq Global Select** ~~exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market~~ **Market** ~~for~~ - **or sanctions** ~~our~~ - **or** ~~common stock and~~ **investigations by the SEC** ~~our~~ - **or** ~~stock price may be more volatile~~ **other regulatory authorities, which would require additional financial and management resources** . We have been, and could in the future be, subject to legal actions and proceedings related to the decline in our stock price, which could distract our management and could result in substantial costs or large judgments against us. The market prices of securities of companies in the biotechnology and pharmaceutical industry, including the market price of our common stock, have been extremely volatile and have experienced fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. In January 2021, a putative class action lawsuit was filed against us and certain of our current and former officers and directors. In July 2021, the lead plaintiff voluntarily dismissed the action without prejudice against all defendants and as to all claims, and this action is no longer pending. Nonetheless, due to the volatility in, or the unfulfilled expectations of stockholders for, our stock price, we may be the target of similar litigation in the future. In connection with such legal proceedings, we could incur substantial costs and such costs and any related settlements or judgments may not be covered by insurance. We could also suffer an adverse impact on our reputation and a diversion of management' s attention and resources, which could cause serious harm to our business, operating results and financial condition. ~~funds,and we may not~~ use these funds effectively,which could affect our results of operations and cause our stock price to decline.Our management will have broad discretion in the application of our existing cash,cash equivalents and marketable securities and could spend these funds in ways that do not improve our results of operations or enhance the value of our common stock.The failure by our management to apply our available funds effectively could result in financial losses that could cause the price of our common stock to decline and delay the development of our product candidates and preclinical programs.Pending their use,we may invest our available funds in a manner that does not produce income or **that loses value.We are** ~~Provisions~~ **111Provisions** in our amended and restated certificate of incorporation and bylaws and Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management. Provisions in our amended and restated certificate of incorporation and bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which our stockholders might otherwise receive a premium for their shares. These provisions also could limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions: ● establish a classified board of directors such that only one of three classes of members of the board is elected each year; ● allow the authorized number of our directors to be changed only by resolution of our board of directors; ● limit the manner in which stockholders can remove directors from the board; ● establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors; ● require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent; ● limit who may call stockholder meetings; ~~108~~ ● authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a stockholder rights plan, or so- called " poison pill, " that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and ● require the approval of the holders of at least 75 % of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our amended and restated certificate of incorporation or bylaws. Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, which prohibits a person who owns in excess of 15 % of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15 % of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. Our amended and restated certificate of incorporation designates the Court of Chancery of the State of Delaware 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 certificate of incorporation provides that, unless we consent in writing to an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for (a) any derivative action or proceeding brought on our behalf, (b) 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, (c) any action asserting a claim arising pursuant to any provision of the Delaware General Corporation Law, our certificate of incorporation or our bylaws or (d) any action asserting a claim that is governed by the internal affairs doctrine, in each case subject to the Court of ~~Chancery~~ **112Chancery** having personal jurisdiction over the indispensable parties named as defendants therein. Any person purchasing or otherwise acquiring any interest in any shares of our capital stock shall be deemed to have notice of and to have consented to this provision of our amended and restated certificate of incorporation. This choice of forum provision is inapplicable to actions arising under the Securities Exchange Act of 1934, as amended, and we likewise do not intend to apply this choice of forum provision to actions arising under the

Securities Act of 1933, as amended. This choice of forum provision may limit a stockholder' s ability to bring a claim that is not arising under the Securities Exchange Act of 1934, as amended, or the Securities Act of 1933, as amended, in a judicial forum that he, she or it finds 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. Stockholders who do bring a claim in the Court of Chancery could face additional litigation costs in pursuing any such claim, particularly if they do not reside in or near the State of Delaware. The Court of Chancery 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 or results may be more favorable to us than to our stockholders. Alternatively, if a court were to find this provision of our amended and restated certificate of incorporation inapplicable to, or unenforceable in respect of, one or more of the specified types of actions or proceedings, we may incur additional costs and business interruption that could have a material adverse effect on our business, financial condition or results of operations. Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be our stockholders' sole source of gain. We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be the sole source of gain for our stockholders for the foreseeable future. ~~109General~~ --- **General** Risk FactorsWe might not be able to utilize a significant portion of our net operating loss carryforwards. As of December 31, ~~2023~~ **2024**, we had both federal and state net operating loss, or NOL, carryforwards of $ ~~55~~ **20**. ~~3~~ **0** million and $ ~~33~~ **0**. ~~2~~ **8** million, respectively. The state NOLs will expire beginning in 2041 while the federal NOLs do not expire. These state NOL carryforwards could expire unused and be unavailable to offset our future income tax liabilities. **The** ~~As described above under the heading " Changes in tax laws or in their implementation or interpretation may adversely affect our business and financial condition, " the~~ TCJA, as amended by the CARES Act, includes changes to U. S. federal tax rates and the rules governing NOL carryforwards that may significantly impact our ability to utilize our NOLs to offset taxable income in the future. Nor is it clear how various states will respond to the TCJA, the Families First Coronavirus Response Act or the CARES Act. In addition, state NOLs generated in one state cannot be used to offset income generated in another state. Furthermore, the use of NOL carryforwards may become subject to an annual limitation under Section 382 of the Internal Revenue Code, or the Code, and similar state provisions in the event of certain cumulative changes in the ownership interest of significant shareholders in excess of 50 percent over a three-year period. This could limit the amount of NOL carryforwards that can be utilized annually to offset future taxable income or tax liabilities. The amount of the annual limitation is determined based on the value of a company immediately prior to the ownership change. Our company has completed several transactions since its inception which resulted in an ownership change under Section 382 of the Code. In addition, future changes in our stock ownership, some of which are outside of our control, could result in ownership changes in the future. For these reasons, even if we attain profitability, we may be unable to use a material portion of our NOLs and other tax attributes. Our internal computer systems, or those of our collaborators or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs. Our internal computer systems and those of our current and any future collaborators and other contractors or consultants are vulnerable to damage from cyber- attacks, computer viruses, unauthorized access, ransom requests, sabotage, natural disasters, terrorism, war and telecommunication and electrical failures. While we have not experienced ~~any~~ **113any** such material system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations or the operations of those third parties with which we contract, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions, and could require a substantial expenditure of resources to remedy. For example, the loss of clinical trial data from completed or ongoing clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. We could also be subject to risks caused by misappropriation, misuse, leakage, falsification or intentional or accidental release or loss of information maintained in our information systems and networks, including personal information of our employees. Outside parties may attempt to penetrate our systems or those of the third parties with which we contract or to fraudulently induce our employees or employees of such third parties to disclose sensitive information to gain access to our data or to use such access to request cash compensation in the form of a ransom for the return of such data. The number and complexity of these threats continue to increase over time. Although we develop and maintain systems and controls designed to prevent these events from occurring, and we have a process to identify and mitigate threats, the development and maintenance of these systems, controls and processes is costly and requires ongoing monitoring and updating as technologies change and efforts to overcome security measures become more sophisticated. Despite our efforts, the possibility of these events occurring cannot be eliminated entirely. Although we maintain cyber risk insurance for certain costs we may incur due to a cyber- related event, this insurance may not provide adequate coverage against potential liabilities. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, or a loss of cash in response to ransom threats, we could incur liability, our competitive and financial position and the market perception of the effectiveness of our security measures could be harmed, our credibility could be damaged, and the further development and commercialization of our product candidates could be delayed. ~~110~~ **114**